









# American Heart Journal

January 1978

An international publication for the study of the circulation

George E Burch Editor

Thomas D Giles Assistant Editor

## International Editorial Board

Walter H Abelmann Boston Mass  
R P Ahlquist Augusta  
James K Alexander Houston Texas  
John B Barlow Johannesburg South Africa  
Giorgio Baroldi Milan Italy  
Lotfi L Basta Tulsa Okla  
Thomas M Blake Jackson Miss  
S Gilbert Blount, Jr Denver  
Bernardo Boskis Argentina  
Eugene I Chazov Moscow U S S R  
Henri Chevalier Paris  
Te Chuan Chou Cincinnati  
J M Crley Torrance Calif  
James A Cronvich New Orleans  
Anthony N Damato Staten Island N Y  
Arthur C DeGraff New York  
Lewis Dexter Boston  
James E Doherty Little Rock  
Charles Dubost Paris  
Jesse E Edwards St Paul  
Robert H Eich Syracuse N Y  
Marty Allen Engle New York  
Harvey Feigenbaum Indianapolis  
M Iréné Ferrer New York  
Nancy C Flowers Louisville  
Nicholas J Fortuin Baltimore Md  
Martin J Frank Augusta Ga  
Julian Frieden New Rochelle N Y  
Peter C Gazes Charleston  
Jacques Genest Montreal Canada  
Allan V N Goodyer New Haven Conn  
Mervyn S Gotsman Jerusalem Israel  
Robert L Grossman Omaha  
Dale Groom Oklahoma City  
Rolf M Gunnar Chicago  
Warren G Gunthorpe Seattle Wash  
E William Hancock Stanford Calif  
Herbert V Hultgren Palo Alto Calif

Mohamed Ibrahim Cairo Egypt  
Thomas N James Birmingham Ala  
L E January Iowa City  
James V Jarnagin Minneapolis  
John A Kator Philadelphia  
Nodar N Kupehidze Tbilisi U S S R  
Richard Langendorf Chicago  
John H Letagh New York  
J Lequime Brussels Belgium  
Maurice Lev Chicago  
R J Lenden Leeds  
F Loogen Dusseldorf Germany  
Hugh A McAllister Jr Washington D C  
Dan G McNamara Houston  
Rashid A Masumi Davis Calif  
Clifford V Nelson Portland Me  
Eckhardt O J Olsen London  
Victor Parsonnet Newark  
Morton Lee Pearce Los Angeles  
Alfred Pick Chicago  
Hubert V Pipberger Washington D C  
Ray Pryor Denver Colo  
E W Reynolds Madison Wisc  
Robert C Schlant Atlanta Ga  
Peter J Schwartz Milano  
Ralph C Scott Cincinnati  
J P Shillingford London  
Walter Somerville London  
Boris Surawicz Lexington  
Tadasu Takatsu O aka  
John Thomas Nashville Tenn  
William H Wehrmacher Chicago  
Hien J J Wellens Maastricht  
The Netherlands  
Douglas P Zipes Indianapolis Ind

Contents on pp 5 7 and 9

ISSN 0002-8703

The C V Mosby Company Publisher  
St Louis Mo 63141 USA



DR. ROBERT HELIG LIBRARY

L 11 L 12

1951

Ac 14028

Dec 24-10-80

*Helig*



# American Heart Journal

January 1978

Copyright © 1978 by The C V Mosby Company

## Contents

### Editorial

The comeback of hydralazine 1  
*Jan Koch Weser MD Strasbourg France*

### Clinical communications

The effects of exercise on the amplitude of the first heart sound in normal subjects 4  
*L Hume MB MRCP and S R Reuben DPhil MB MRCP Edinburgh Scotland*

The orthogonal electrocardiogram in normal women Implications of sex differences in diagnostic electrocardiography 12  
*Massoud Nemati MD Joseph T Doyle MD Donald McCaughan MD Rosalie A Dunn PhD and Hubert V Pipberger MD Washington D C*

Antegrade and retrograde conduction characteristics in three patterns of paroxysmal atrioventricular junctional reentrant tachycardia 22  
*Masood Akhtar MD Anthony N Damato MD Jeremy N Ruskin MD William P Batsford MD C Pratap Reddy MD Andres R Ticzon MD Walhail S Dhatt MD Joseph A C Gomes MD and Antonino H Calo MD Staten Island N Y*

### Experimental and laboratory reports

A possible role of noradrenaline in the development of myocardial infarction An experimental study in the isolated rat heart 43  
*Anders P Waldenström Ake C Hjalmarson and Lars Thornell Göteborg and Umeå Sweden*

*continued on page*

Vol. 95 No. 1 January 1978 The American Heart Journal is published monthly by The C V Mosby Company 11630 Westline Industrial Drive St. Louis, Mo. 63141

### Annual subscription rates

	US	PUAS Mexico	Canada other countries
Institutional	\$37.00	\$43.50	\$44.50
Personal	\$ 4.00	\$30.50	\$31.50
Student, read only	\$19.20	\$25.70	\$26.00

(For information of the American and Spanish)

Single copies are \$4.00 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Individual (multiple read only) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and professional institutions and organizations.

Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals. All student rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.

Printed in the U.S.A. copyright © 1978 by The C V Mosby Company



Components of the hemodynamic response to elevated cerebrospinal fluid pressure 52

*Richard E Brashear M.D. and Pao lo Yu Ph.D Indianapolis Ind.*

Functional properties of the left septal Purkinje network in premature activation of the ventricular conduction system 60

*Nobuyuki Icamura M.D Itsuo Kodama M.D Takeshi Shimizu M.D., Yukio Hirata M.D Junji Toyama M.D and Kazuo Yamada M.D Nagoya Japan*

Detection of myoglobin by radioimmunoassay in human sera Its usefulness and limitations as an emergency room screening test for acute myocardial infarction 70

*Gary Gilheson B.S Martin J Stone M.D Michael Waterman Ph.D Ruby Ting M.A Celso E Gomez-Sanchez M.D Alan Hull M.D and James T Willerson M.D F.A.C.C Dallas Texas*

Effect of saralasin upon plasma catecholamines in hypertensive patients 78

*Nicolas D Vlachakis M.D Arthur B Ribeiro M.D and Laurence R Arakoff M.D New York N Y*

## Case reports

Relationship between myocardial infarction and preinfarction angina A histopathological study of coronary arteries in two sudden death cases employing serial section 81

*Toshinobu Horie M.D Morie Sekiguchi M.D and Koshichiro Hirotsugu M.D Tokyo Japan*

Hereditary bundle branch system defect Survey of a family with four affected generations 89

*Edouard Stephan M.D Beirut Lebanon*

## Review

Use of precordial ST segment mapping 96

*John E Nadias M.D Boston Mass*

## Fundamentals of clinical cardiology

Concepts and applications of treadmill exercise testing and the exercise electrocardiogram 102

*James V Farris M.D Paul L McHenry M.D and Stephen N Morris M.D Indianapolis Ind*

## Appraisal and reappraisal of cardiac therapy

Cardiac pacing and pacemakers IX Statistical analysis of pacemaker data 115

*Seymour Furman M.D and Richard Whitman B.E.C.C.E Bronx N Y*

## Annotations

Single coronary artery with myocardial infarction and mitral regurgitation 126

*Maury C Newton Jr M.D and Laurence R Burwell M.D Charlottesville Va*

Of plastic materials in clinical medicine 127

*G E Burch M.D New Orleans La*

Myocardial edema a complication of ischemic arrest during cardiopulmonary bypass 128

*Richard M Engelman M.D Chicago Ill*

continued on page 9



**Contents continued**

**Diet in the Coronary Care Unit 130**

*S E Warren Lt MC USNR J S Alpert Lt Cdr MC USNR and G S Francis  
Lt Cdr MC USNR San Diego Calif*

**Letters to  
the Editor**

**Effect of vagus nerve stimulation on ventricular fibrillation  
threshold 132**

*Benet S Holman M.D Richard L Verner Ph.D and Bernard Loun M.D  
Boston Mass*

**Reply 132**

*Jaok Han M.D Ph.D and Myung S Yoon M.D Albany N Y*

**Wolff Parkinson White (Type B) Ebstein's anomaly and congenital  
ichthyosis 133**

*Morris M Weiss M.D F.A.C.C. F.A.C.P Louisville Ky*

**Venture research 133**

*Stephen Seely B.Sc Sale Cheshire England*

**Potassium and salt substitutes 134**

*Ali Haddad M.D Iron Mountain Mich*

**Computerized electrocardiography 135**

*Leon Fordy M.D F.A.C.C New York N Y*

**Book reviews**

**Book reviews 136**

**Books received**

**Books received 137**

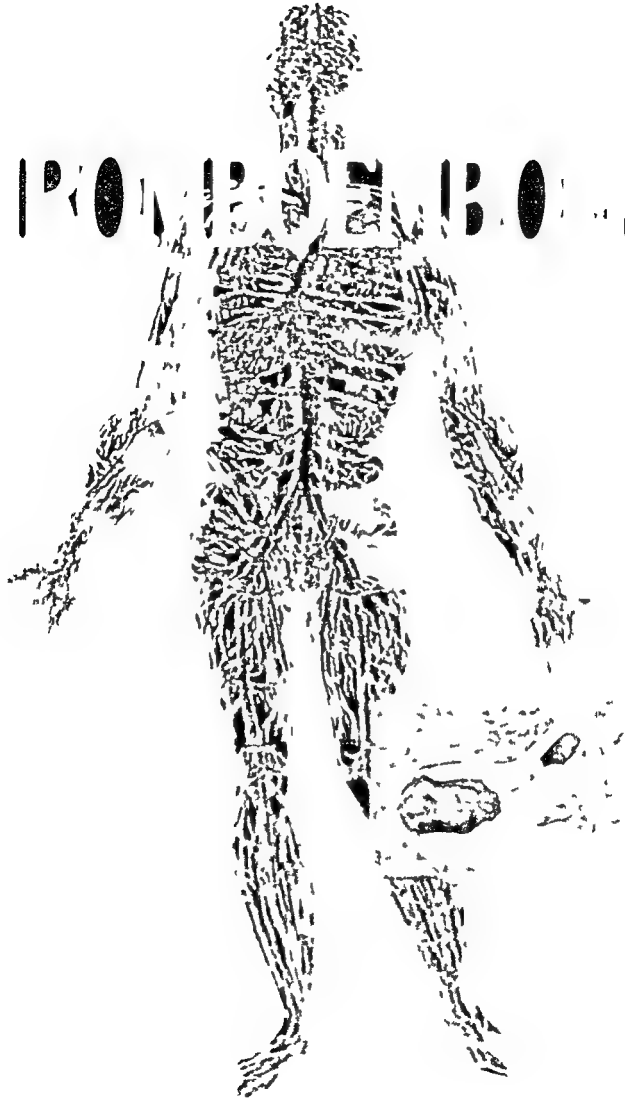
**Announcements**

**Announcements 138**

*(Information for authors on page 13)*



# PROMETHEUS



# American Heart Journal

February 1978

Copyright © 1978 by The C V Mosby Company

## Contents

### Editorial

Can death from venous thromboembolism be prevented in elderly patients with hip fractures 139

C Keith Morris MD and J R A Mitchell MD Nottingham England

### Clinical communications

Intrapulmonary acetylcholine in bilateral cor pulmonale 141

M M Abdel Fattah MD A Abou Zenia MD A M Vomeir MD H Badawi MD and M Salah FRCP Alexandria Egypt

Cardiac reserve during isoproterenol stress in patients with aortic valve disease before and after corrective surgery 148

Fran Schuur MD Willem Flameng MD Jochen Thormann MD Roland Ensslen MD Michael Sesto MD and Martin Schlepper MD Bad Nauheim and Giessen West Germany

Clinical classification of Ebstein's anomaly 154

Shunsuke Takarazu MD Yo-hio Obunai MD and Souji Konno MD Tokyo Japan

Polymicrobial infective endocarditis An increasing clinical entity 163

L D Saravolatz MD K H Burch MD E L Quinn MD F Cox MD T Madhavan MD and E Fisher MD Detroit Mich

Abrupt propranolol withdrawal in angina pectoris Effects on platelet aggregation and exercise tolerance 169

William H Frishman MD James Christodoulou MD Babette Weksler MD Charles Smith MD Thomas Kilup MD and Stephen Scheldt MD New York NY

continued on page 7

Vol 86, No 2, February 1978. The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St. Louis, Mo 63141

### Annual subscription rates

	U.S.	PUAS Mexico	Canada other countries
Institutional	\$37.00	\$47.50	\$44.50
Personal	\$4.00	\$30.00	\$31.00
Student resident	\$19.00	\$25.00	\$26.00

(Postal Union of the Americas and Spain)

Single copies are \$1.50 postage free. Back issues should be ordered by check or draft post office or express money order payable to this Journal.

Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and universities, county, state, provincial, and national government bureaus and departments, and all commercial and professional associations and organizations.

Personal subscriptions and all student rate subscriptions must be in the names of individuals and paid by individuals. All student rate requests must indicate training status and name of institution. Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.

Printed in the U.S.A. Copyright © 1978 by The C V Mosby Company.

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 65, Schenectady, NY 12301, 518-374-4330 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

A reminder  
**LANOXIN<sup>®</sup>**  
 (digoxin)



A reminder  
 to take your  
 digoxin  
 as directed  
 by your doctor  
 to keep your heart  
 healthy.

Lanoxin<sup>®</sup> Tablets  
 0.25 mg. and 0.5 mg.  
 Tablets

## Contents continued

### The variability of arterial pressure 180

W A Little M.D. MRCP M J West M.B. Ph.D. MRACP A J Honour  
M.A. D.Phil. and P Sleight M.D. FRCP Oxford England

### The systolic time intervals in thyroid dysfunction 187

Dieter Burckhardt M.D. Jean-Jacques Staub M.D. Martin Kraenzlin M.D.  
Ernst Roeder M.D. Urs Engel M.D. and Peter Cloppenburg M.D. with the  
technical assistance of Priska Boschung Basel Switzerland

## Experimental and laboratory reports

### The effects of psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog 197

Regis A. DeSilva M.B. FRCP(C) Richard L. Verrier Ph.D. F.A.C.C. and  
Bernard Lown M.D. F.A.C.C. Boston Mass

### Post extrasystolic potentiation of ischemic myocardium by atrial stimulation 204

George A. Diamond M.D. James S. Forrester M.D. Protasio L. deLuz M.D.  
H L Wyatt Ph.D. and H J C Suan M.D. Ph.D. Los Angeles Calif

### Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease 210

B E Strauer and A Scherpe Munich W. Germany

### The difference vector Assessment of effects of changes or interventions 220

Clifford V. Nelson Ph.D. Brian C. Hodgkin Ph.D. R. Alan Bonner D.V.M. Ph.D.  
and Evangelos T. Angelakos M.D. Ph.D. Portland Me

### Effects of proximal intra atrial Wenckebach on distal atrioventricular nodal and His Purkinje block With special reference to the theory of alternating Wenckebach periods 228

Agustin Castellanos M.D. Ruey J. Sung M.D. Stephen M. Mallon M.D. Martin  
G. Bloom M.D. and Robert J. Myerburg M.D. Miami Fla

## Case reports

### Misdiagnosis of atrial septal defect in patients with hereditary telangiectasia (Osler Weber Rendu disease) and hepatic arteriovenous fistulas 235

Wallace E. Radtke M.D. Hugh C. Smith M.D. Richard E. Fulton M.D. and  
Martin A. Adson M.D. F.A.C.S. Rochester Minn.

### Pulmonary varix Report of a case with additional anomalies of the vascular pulmonary tree 243

C. Moro E. Warrn A. Sanchez and J. Solozabal Madrid Spain

## Clinical pathologic conference

### Clinical pathologic conference 247

David H. Spodick M.D. Irwin K. Alme M.D. Arthur J. Press M.D. A. N.  
Voghadam M.D. Riaz A. Akh'ar M.D. and Leonard S. Dreyfus M.D. Philadelphia  
Pa. and Worcester Mass

## Fundamentals of clinical cardiology

### The role of the central nervous system in chronic congestive heart failure 255

G. E. Burch M.D. New Orleans La

A reminder  
**LANOXIN®**  
(digoxin)



SECRET

## Contents continued

### Appraisal and reappraisal of cardiac therapy

#### Annotations

#### Prazosin 262

*Jerome Louenstein M.D. and John M Steele Jr M.D. New York N.Y.*

#### Rheumatic heart disease psittacosis and the importance of epidemiology 266

*Christopher Ward M.D. M.R.C.P. Sheffield England*

#### On the significance of an abnormal P terminal force in Lead V<sub>1</sub> 267

*P.A.N. Chandraratna M.D. M.R.C.P. and Eugene Langerin D.O. Oklahoma City Okla.*

#### Analgesic abuse and microvascular changes 268

*C. Abrahams F.R.C.Path. F.F.Path(SA) & I. Furman F.R.C.P.(Edin) and D. Salant F.C.P.(SA) Johannesburg South Africa*

#### Of the mind of man 269

*G.E. Burch M.D. New Orleans La.*

#### Differences in Coronary Care Units 270

*M. Noel O'Rourke M.D. F.R.A.C.P. Darlinghurst N.S.W. Australia*

#### Differential refractoriness of ventricular specialized conduction system 270

*J. Tenezer M.D. and L. Littmann M.D. Budapest Hungary*

#### Arterial thromboembolic complications with aortic ball valve prostheses 270

*M.J. Boekhout M.ussert E. Briet P. van Brummelen H.H.P.J. Lemkes and F.A. Loeliger Leiden The Netherlands*

#### Reply 271

*Jon Dale Oslo Norway*

#### More on high school health curricula 272

*Ralph L. LaForge M.Sc. Albuquerque N.M.*

#### Nitroglycerin ointment therapy and leg edema 273

*St. George T. Lee Jr M.D. Charlottesville Va.*

#### References—dogs tails? 274

*Richard J. Kennedy M.D. New York N.Y.*

#### Chromosome aberration in ectopia cordis (46 XX 17q+) 274

*Burhan Say M.D. and Carla E. Wiley M.D. Tulsa Okla.*

#### Excitation contraction abnormalities and heart block 275

*Asum Istanbullu M.D. London England and Suha Yeldet M.D. Istanbul Turkey*

#### Aortic valve prostheses rheumatic fever and lone aortic regurgitation 275

*Howard H. Kloth M.D. F.A.C.C. F.C.C.C. New York N.Y.*

#### Book reviews

#### Books received

#### Announcements

#### Book reviews 277

#### Books received 278

#### Announcements 278

*(Information for authors on page 13)*



## Contents

### Editorial

International cardiology 279

J F Goodwin MD London England

### Clinical communications

Sequence of cardiac changes in Duchenne muscular dystrophy 283

S B Heymsfield T McNish J V Perkins and J M Felner Atlanta Ga

Ondine's Curse Hemodynamic response to diaphragm pacing (electrophrenic respiration) 295

Rene A Langou MM Laurence S Cohen MD David Sheps MD Steven Wolfson MD and William W L Glenn MD New Haven Conn

Measurement of the circulatory effects of dobutamine: a new inotropic agent in patients following cardiac surgery 301

G R J Lewis MRACP MRCP PA Poole Wilson MD MRCP T A Angerpointer MD A E Farnsworth FRCS B T Williams FRCS and D J Coltart MD MRCP FACC London England

Prediction of aortic valvular area and gradient by noninvasive techniques 308

A Lucian Cousins MD E E Eddleman Jr MD and T Joseph Reeves MD Birmingham Ala

continued on page 7

Vol 95 No 3, March, 1978 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St Louis, Mo 63141

### Annual subscription rates

	U.S.	P.O. Box Mexico	Canada other countries
Individual	\$3.00	\$12.50	\$44.50
Personal	\$4.00	\$10.50	\$31.50
Student reader	\$19.00	\$5.00	\$6.00

(Postal Union of the Americas and Spain)

Single copies are \$4.00 postpaid. Remittances should be made by check or draft payable to the order of the publisher.

Institutional (multiple) subscriptions are available at a special rate for hospitals, clinics, county health departments, and libraries. Single copies are available at a special rate for individuals. All subscription rates are in U.S. dollars.

Subscription orders must be in the name of the billed to and paid by individual. All subscription requests must include the name of the institution and the name of the institution.

Second class postage paid at St. Louis, Mo., and additional mailing offices. Printed in the U.S.A. Copyright © 1978 by The C V Mosby Company.

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 27 Congress St., Salem, MA 01970. This consent does not extend to other kinds of copying, such as that for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.





**Histopathology of the conducting tissue of the heart in Chagas myocarditis 316**

*Zilton A Andrade MD Sonia M Andrade MD George B Oliveira MD and Daniel R Alonso MD Bahia Brazil and New York N Y*

**Total effective compliance of the vascular bed in essential hypertension 325**

*G M London MD M E Safar MD Y A Weiss MD and Ch A Simon MD Paris France*

**Effect of pentobarbital anesthesia on ventricular defibrillation threshold in dogs 331**

*Charles F Babbs MD MS West Lafayette Ind.*

**Comparison of coronary arteriograms with direct measurements of stenosed coronary arteries in dogs 338**

*Kim P Gallagher PhD John M Folts PhD and George G Roue MD With the technical assistance of Ronald Shebush Madison Wisc*

**The incidence and significance of contraction bands in endomyocardial biopsies from normal human hearts 348**

*Gerald E Adomian PhD Michael M Laks MD and M E Bilingham MD Torrance and Stanford Calif*

**Creatine phosphokinase MB isoenzyme in hypothermia Case reports and experimental studies 352**

*C Jeffrey Carlson MD Bianca Emulson and Elliot Rapaport MD With the technical assistance of Mr Leslie Bible San Francisco Calif*

**Case reports**

**The prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis 359**

*Charles D Johnson MD and F Martinez Catuche MD Rio Piedras Puerto Rico*

**Isolated T wave alternans 369**

*Francisco Natarro Lope MD FACC Juan Cinca MD Gines Sanz MD Alberto Perez MD Jorge Magrina MD and Amadeo Betru MD Barcelona Spain*

**Review**

**Clinical biochemical and pathological features of low renin ( primary ) hyperaldosteronism 375**

*J B Ferriss D G Beevers J J Brown D L Davies M Fraser A F Leiper P Mason A M Neill and J I S Robertson Glasgow Scotland and London England*

**Fundamentals of clinical cardiology**

**The hypertension complex 389**

*Milton Mendlovic MD New York N Y*

**Appraisal and reappraisal of cardiac therapy**

**The functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance collateral flow 396**

*Michael V Cohen MD Bronx N Y*

**Annotations**

**Fibrin deposition on a pacemaker catheter in a heparinized patient 405**

*Robert W MacMillan MD Major USAF MC and Randall W Strate MD Major USAF MC Washington D C*

continued on page 9



Of diastolic and systolic pressure and left ventricular work 406

*G E Burch M.D. New Orleans La*

At home or to hospital? 406

*R J Donaldson MB D.P.H. FF.C.M. London England*

Electromagnetic interference in dynamic electrocardiography caused by an electric blanket 408

*Joseph A Gascho M.D. Iowa City and Maury C Neuton Jr MD Marietta Ga*

Mechanism of concealed trigeminy 410

*Shunji Kinoshita MD Sapporo Japan*

Reply 411

*Matthew N Levy M.D. Cleveland Ohio*

Indirect recording of left atrial activation in the main pulmonary trunk 412

*P Puech M.D. Montpellier France*

Reply 413

*Fernando Amat y Leon M.D. and Kenneth M Roven MD Chicago Ill*

Preceptorships at major medical centers 413

*Philip H Livingston M.D. Chattanooga Tenn*

Sudden deaths from IHD by age and sex 413

*Richard M Hodes BA Fairbanks Alaska*

Book reviews 414

Books received 415

Announcements 416

*(Information for authors on page 13)*

Letters to  
the Editor

Book reviews

Books received

Announcements



## Contents

## Editorial

## Natural fibrinolysis 417

Norman L Brouse MD FRCS (Eng) London England

## Clinical communications

## Autonomic maneuvers in hereditary Q T interval prolongation (Romano Ward syndrome) 420

Eduard I Curtiss MD FACC Richard H Heibel MD and James A Shaler MD FACC Pittsburgh Pa

## Significance of new Q waves after bypass grafting Correlations between graft patency ventriculogram and surgical venting technique 429

Agop Aintablian MD Robert I Hamby MD Irwin Hoffman MD Daniel Weiss MD Chondary Voletti MD and R George Wisoff MD Neu Hyde Park Jamaica and Stony Brook N Y

## Silent myocardial ischemia during and after exercise testing in patients with coronary artery disease 441

H Eugene Lindsey Jr MD and Peter F Cohn MD Boston Mass

continued on page 7

## Annual subscription rates

Vol. 85 No. 4 April, 1978 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Dr St. Louis Mo 63141

	U.S.	P.U.A.S. Mexico	Canada other countries
Institutional	\$37.00	\$43.50	\$44.50
Personal	\$ 4.00	\$30.50	\$31.50
Student, resident	\$19.20	\$4.50	\$4.50

(Post 1 Union of the Americas and Spain)

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.

Foreign (subscriptions and all student rates) subscriptions must be in the names of libraries and paid by institutional bill. All student rate requests must indicate training status and name of institution. Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.  
Printed in the U.S.A. copyright © 1978 by The C V Mosby Company

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 6, Schenectady, N.Y. 12301, \$18.75 + \$4.00 for copying beyond that permitted by Section 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale.



## Contents continued

### Bacterial endocarditis: An analysis of factors affecting long term survival 448

A Mills McNeill PhD MD James E Strong Jr MD and W R Lockwood MD Jackson Miss

### Influence of etiology on the functional result of aortic valve replacement 454

K F Hossack MRACP and Graeme Neilson FRACP FRCP Brisbane Australia

### Coronary artery spasm and mitral valve prolapse 457

A J Buda MD D L Letene MD M G Myers MD A W Chisholm MD and S J Shane MD Toronto Ontario Canada

### Electrode position effects on Frank lead electrocardiograms 463

Alan S Berson PhD W Kenneth Haisty MD and Hubert V Pipberger MD Washington D C

### Lidocaine induced cardiac rate changes in atrial fibrillation and atrial flutter 474

Doniel T Danahy MD and Wilbert S Aronow MD Long Beach and Irvine Calif

### Cholelithiasis: A frequent complication of artificial heart valve replacement 483

Earl C Harrison MD F John Roschke PhD Harley I Meyers MD W Allan Edmiston MD Linda S Chan PhD Dorothy Taffler MD and Francis Y A Lau MD Los Angeles and Pasadena Calif

### The influence of atrial systole on ventricular capture by failing artificial pacemakers II: Experimental observations 489

William S Abernathy MD Gregory R Ferrer PhD and Gordon A Moe MD PhD Lima N Y

### Systemic hypertension after surgical treatment of a congenital arteriovenous malformation 497

Albert P Rocchini MD Amnon Rosenthal MD Samuel Schuster MD Kenneth E Fellous Jr MD and Alexander S Nadav MD Boston Mass

### The influence of atrial activity on ventricular capture by failing artificial pacemakers I: Report of two new cases and review of the literature 502

William S Abernathy MD and E Lepechkin MD Lima N Y and Burlington Vt

### A discussion on hypertrophic cardiomyopathy 511

Thomas L Spray MD Barry J Varon MD Andreu G Morrow MD Stephen E Epstein MD and William C Roberts MD Bethesda Md

### Creatine kinase isoenzymes in the assessment of heart disease 521

Robert Roberts MD and Burton E Sobel MD St Louis Mo

### Management of shock following acute myocardial infarction Part I: Drug therapy 529

Leslie A Kohn MD New York N Y

## Experimental and laboratory reports

## Case reports

## Clinical pathologic conference

## Fundamentals of clinical cardiology

## Appraisal and reappraisal of cardiac therapy



A reminder  
**LANOXIN<sup>®</sup>**  
(digoxin)



By

Georgetown University School of Medicine  
Washington, D.C. 20007

**Annotations**

**Of teaching hygiene 535**

*G E Burch M.D. New Orleans La*

**The problem of cell aggregation during coronary artery bypass procedures 535**

*Bernard Ecanow Ph.D. and Bernard H Gold Ph.D. Chicago Ill*

**To each according to his desert 536**

*David Scherf M.D. and Jules Cohen M.D. New York N Y*

**Statistics marathoning and CHD 538**

*Paul Wily Ph.D. New York N Y*

**Letters to  
the Editor**

**Needed An F D A for surgery? 540**

*Myron R Schoenfeld M.D. Scarsdale N Y*

**Fructose and triglycerides 540**

*M J Halpern Lisbon Portugal*

**Salvage the pacemaker at autopsy 540**

*Lino Rossi Milan Italy*

**Reactions to furosemide 541**

*Lieutenant S E Warren (MC) USNR and Commander S M Steinberg (MC) USN  
San Diego California*

**Reply 542**

*David J Greenblatt M.D. Waltham, Mass*

**Book reviews**

**Book reviews 543**

**Books received**

**Books received 544**

**Announcements**

**Announcements 544**

*(Information for authors on page 13)*



## Contents

- Editorial** Ventricular afterload: a succinct yet comprehensive definition 545  
*Abraham Noordergraaf Ph.D. M.A. and Jules Melbin M.D. Ph.D.*  
 Philadelphia Pa
- Clinical communications** Echocardiographic features of the normal and malfunctioning porcine xenograft valve 548  
*P. A. N. Chandrasekhar M.D. M.R.C.P. and S. B. San Pedro M.D.* Oklahoma City Okla
- Arrhythmias and the Holiday Heart: Alcohol associated cardiac rhythm disorders 555  
*Philip O. Ettinger M.D. Chia F. Wu M.D. Catalino De La Cruz Jr. M.D. Allen B. Weiss M.D. S. Sultan Ahmed M.D. and Timothy J. Regan M.D.* Newark and Englewood N.J.
- Angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis 563  
*Bernadine H. Bulkley M.D. Peter G. Klatzmann M.D. and Grover M. Hutchins M.D.* Baltimore Md

continued on page 7

## Annual subscription rates

Volume 9, Number 5, May 1978. The American Heart Journal is published monthly by The C V Mosby Company, 11870 Westline Industrial Drive, St. Louis, Mo. 63141.

	U.S.	Puerto Rico Mexico	Canada other countries
Institutional	\$37.00	\$41.50	\$44.50
Personal	\$24.00	\$30.50	\$31.50
Student resident	\$19.00	\$ 0	\$ 0

(Postal List of the American and Spanish)

Single copies are \$4.00 postpaid. Remittances should be made by check, draft, post office or express money order payable to this journal.

Institutional (multiple) and student subscription rates are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.

Personal subscription and all student rates are subject to the provisions of the bill of lading and paid by individuals. All student rates require a letter of recommendation from a faculty member of the institution.

Subscription may begin any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.

Printed in the U.S.A. Copyright © 1978 by The C V Mosby Company.

The appearance of a code at the bottom of the first page of an original article in this journal indicates that copyright clearance has been arranged. This code indicates that the article may be reproduced for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 27 Congress St., Salem, MA 01970. This consent does not extend to other kinds of copying, such as that for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840.



The purpose of this study was to determine the effect of the use of a computer-aided instruction (CAI) program on the learning of the basic concepts of the cell and the process of photosynthesis in a biology class. The study was conducted in a biology class in a high school in the city of San Jose, Costa Rica. The class was divided into two groups: a control group and an experimental group. The control group received traditional instruction, while the experimental group used the CAI program. The results of the study showed that the experimental group performed significantly better than the control group on a post-test. This suggests that the use of a CAI program can be an effective method for teaching basic concepts in biology.



**The HCNAX Family  
of Self-Anchoring Leads**  
10000116 Electronic

**Our culture**

1000-7702/00/0000-0000\$10.00/0

[illegible]

4. united nations      5. majority of the world's population

101

**Contents continued**

**Effect of coronary collaterals on left ventricular function at rest and during stress 570**

*Fran. Schwarz M.D. Willem Flameng M.D. Roland Ensslen, M.D. Michael Sesto M.D. and Jochen Thormann M.D. Bad Nauheim West Germany*

**Echocardiography in chronic alcoholics following prolonged periods of abstinence 578**

*William C Reeves M.D. Nasir L. Nanda M.D. and Raymond Gramiak M.D. Rochester N.Y.*

**Cardiac abnormalities in cachectic patients before and during nutritional repletion 584**

*Steven B. Heymsfield M.D. Robert A. Bethel M.D. Joseph D. Ansley M.D. Daniel W. Gibbs M.D. Joel W. Felner M.D. and Donald O. Nutter M.D. F.A.C.P., Atlanta Ga.*

**Hemodynamic evaluation of the Ionescu Shiley pericardial xenograft in the mitral position 595**

*Anand P. Tandon M.D. M.R.C.P. Donald R. Smith M.D. F.R.C.P. and Marian I. Ionescu M.D. F.A.C.S. Leeds England*

**Human pharmacology studies with a new, orally active stimulant of cardiac adrenergic beta receptors 602**

*M. Anas M.D. B. Pfister M.D. U. C. Dubach M.D. and P. R. Imhof M.D. Basel Switzerland*

**Mechanism of antihypertensive effect of thiazide diuretics 611**

*Ashrafat Shah M.D. Ibrahim Khatri M.D. and Eduard D. Freis M.D. Washington D.C.*

**Changes in components of kinin system and hemodynamics in acute myocardial infarction 619**

*Akio Hoshimoto M.D. Hiromu Hamamoto M.D. Yuchiro Honda M.D. Masaru Hirose M.D. Soichi Furukawa M.D. and Eichi Kumura M.D. Tokyo Japan*

***Chlamydia trachomatis* endocarditis 627**

*Johanna M. van der Bel Kahn M.D. Chatrchas Watanakunakorn M.D. Max G. Venefer M.D. Ph.D. Herbert D. Long M.D. and Richard Dieter M.D. Cincinnati Ohio*

**Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia Report of a patient with normal coronary arteriograms 637**

*Amol A. Chavla M.D. F.A.C.C., F.R.C.P.(C) Jairo Cruz M.D. Neil E. Kramer M.D. F.A.C.C. and William D. Toune M.D. F.A.C.C. F.A.C.P. F.C.C.P. Chicago Ill.*

**Low renin ( primary ) hyperaldosteronism Differential diagnosis and distinction of sub groups within the syndrome 641**

*J. B. Ferras D. G. Berlet J. J. Brown R. Fraser A. F. Lever P. L. Padfield and J. I. S. Robertson Glasgow Scotland*

**Radionuclides in the assessment of myocardial infarction 659**

*Wilton S. Alton M.D. Robert Roberts M.D. and R. Edward Coleman M.D. St. Louis Mo.*

**Radionuclides in the assessment of myocardial infarction 659**

*Wilton S. Alton M.D. Robert Roberts M.D. and R. Edward Coleman M.D. St. Louis Mo.*

**Experimental and laboratory reports**

**Case reports**

**Review**

**Fundamentals of clinical cardiology**

# Do you really think a mere ocean is going to stop us from giving you great service?

Vitatron Europe's largest pacemaker manufacturer is in America.

You probably know all about our lithium iodine pacemaker Vitralith™ with the slightly incredible service life of 12 years.\*

You've probably also heard about our absolutely uncompromising dedication to reliability.

But even after knowing all of this, is it possible that you may still be a little reluctant about doing business with a company so far away?

After all, what happens when you need a little service? Or when you just want to consult with someone on a particular pacing application?

What we'd like you to know is, we can give you all of that. And more. We're not really as far away as you think. Our American headquarters is right here in Boston.

It's there to help our customers wherever and whenever they need it. In fact, we guarantee one of our Pacemaker Service Consultants will be available to assist with any problem or answer any question you may have — 24 hours a day, 365 days a year.

So don't worry that we're in Europe. Because if it's one thing we're not about to let happen, it's to have our good service wind down like a beach toy when you're as far away as you are.

For information, write Vitatron Medical Inc., One Gateway Center, New Bedford, MA 02199. Or call 1-800-779-6641. In Europe, Vitatron Medical has a PO Box 76, NL 6210 DD, in The Netherlands.



## Contents continued

### Appraisal and reappraisal of cardiac therapy

A plea for early open mitral commissurotomy 668  
*Frank C Spencer M.D., New York N Y*

### Annotations

Increase of WBC CRP and BSR following cardiac pacemaker  
implant 671

*Masayoshi Yokoyama M.D Tokyo Japan*

Significance of nausea and vomiting during acute myocardial  
infarction 671

*S Sultan Ahmed M.D FRCP(C) FACC R C Gupta M.D and Russell R  
Brancato M.D Newark N J*

A unique antibody response associated with the development of  
membranous nephropathy in systemic lupus erythematosus 672

*Peter S Friend M.D Minneapolis Minn*

Of the sham operation 674

*George E Burch M.D New Orleans La*

### Letters to the Editor

Menstruation and heart disease 675

*Michael Goodyear Melbourne Australia*

Blood donors and coronary disease 675

*Stephen Seely B.Sc Sale Cheshire England*

Overdiagnosis of left anterior hemiblock 675

*Otto Neurath M.D Newark N J*

Retrograde Wenckebach phenomenon in ventricular tachycardia 676

*S Cotoi C Georgescu and P Coslea Tirgu Mures Romania*

### Book reviews

Book reviews 677

### Books received

Books received 678

### Announcements

Announcements 678

*(Information for authors on page 13)*





**Contents****Editorial**

Inferior vena caval interruption in the prevention of fatal pulmonary embolism 679

A M N Gardner DM MCh FRCS Newton Abbot Devon England

**Clinical communications**

Non specific aorto arteritis in Singapore with special reference to hypertension 683

P C Teoh MB MMed MRCP MRACP FCCP L A A Tan MB DMRD FRCP B L Chia MB FRACP, FACC T C Chao MB DMJ DPath FCIM FRCPA FCAP J A Tambyah MB FRACP and P H Feng MB FRCP(G) Singapore Singapore

Myocardial infarction in the Black population of South Africa  
Coronary arteriographic findings 691

Elhot Chesler MD FRCP FACC Abdul S Mitha MRCP (UK) E Kenneth Weir DM (Oxon) MRCP (UK) Rodney E Mahson MB ChB FCP (SA) and Peter J Hitchcock MB FCP (SA) Natal South Africa

Four year follow up of Black schoolchildren with non ejection systolic clicks and mitral systolic murmurs 697

Morris Cohen MB Wendy A Pocock MB Jeffrey B Lahier MD Margaret J McLaren MB Anthony S Lockman MB and John B Barlow MD Johannesburg South Africa

*continued on page 7*

Vol III No 6 June 1978 The American Heart Journal is published monthly by The C V Mosby Company 11530 Westline Industrial Drive St Louis, Mo 63141

**\* Annual subscription rates**

|                  | U.S.    | P.U.S.<br>Mexico | Canada other<br>countries |
|------------------|---------|------------------|---------------------------|
| Institution 1    | \$37.00 | \$43.00          | \$44.50                   |
| Persons 2        | \$ 4.00 | \$30.50          | \$31.50                   |
| Student, non 1st | \$19.20 | \$ 5.50          | \$ 6.00                   |

(Postal Union of the Americas and Spain)

Single copies are \$4.00 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Institutional (non title reader) subscriptions are available to public and private libraries, schools, hospitals, and church, city, county, state, provincial and national government bureaus and departments and all commercial and private institutions and organizations.

Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals. All student rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.  
Printed in the U.S.A. copyright © 1978 by The C V Mosby Company

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 65, Schenectady, NY 12301 518-538-4630 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

# For a more efficient Ventilation in 1

The Ventilation of the house is one of the most important factors in the health of the family. It is the only way to get rid of the stale air and replace it with fresh air. The Ventilation of the house is one of the most important factors in the health of the family. It is the only way to get rid of the stale air and replace it with fresh air.



# For a more efficient Ventilation in 2

The Ventilation of the house is one of the most important factors in the health of the family. It is the only way to get rid of the stale air and replace it with fresh air. The Ventilation of the house is one of the most important factors in the health of the family. It is the only way to get rid of the stale air and replace it with fresh air.



**THE BURNING Family**  
**ON SAFETY OF DRUGS**  
**THIS CONTAINS DRUGS**

**Our first**  
**Tip**

**Contents continued**

**Significance of a terminal R wave in Lead V<sub>1</sub> of the electrocardiogram 702**

*H Raunio MD, I Rissanen MD, C Jokinen MD and O Penttilä MD  
Kuopio Finland*

**Evaluation of the heart rate response to the Valsalva maneuver 707**

*John H Kalbfleisch PhD, David F Stone PhD and James J Smith MD  
PhD Milwaukee and Wood Wis*

**Involvement of the cardiac conduction system in panarteritis nodosa 716**

*Goetano Thiene MD, Marieluisa Valente MD and Lino Rossi MD  
Padua and Milan Italy*

**Experimental and laboratory reports**

**Vagal tone: significance of electrophysiologic findings and clinical course in symptomatic sinus node dysfunction 725**

*Jochen Thormann MD, Franz Schwarz MD, Roland Ensslen MD and Michael Sesto MD  
Bad Nauheim West Germany*

**Differences in metal content of the heart muscle in death from ischemic heart disease 732**

*Borbara Chipperfield MA PhD and J R Chipperfield MA PhD  
Hull England*

**The effect of chronic cardiac denervation on infarct size following acute coronary occlusion 738**

*Carl E Jones PhD, Michael D DeGous Sr PhD, John Y Thomas Jr PhD and Elsie DuPont BS  
College Station Texas*

**The significance of hypotension developing during treadmill exercise testing 747**

*Rafael Lettier MD, FACC, Thomas Baker MD and Gary J Anderson MD  
FACC Philadelphia Pa*

**Carbon monoxide and ventricular fibrillation threshold in dogs with acute myocardial injury 754**

*Wilbert S Aronow MD, Eduard A Stemmer MD, Byron Wood MD, Stephen Zweig MD, Ke-ping Tsao MD and Louis Raggo  
Long Beach and Irvine Calif*

**Case reports**

**Acute postoperative graft phlebitis: A rare cause of saphenous vein-coronary artery bypass failure 757**

*Bernadine H Bulkeley MSc and Grover W Hutchins MD  
Baltimore Md*

**Simulated tricuspid valve echoes in tricuspid atresia 761**

*Norman H Silverman MD, Maurice Pavot MD and Paul Stanger MD  
San Francisco Calif*

**Massive myocardial necrosis in a young woman 766**

*Rugoudas Venkatas MD, David Fishman MD, Thomas Allip MD, Willard Dallon MD, Cissur Brynjolfsson MD, John Robinson MD and Rolf W Gunnar MD  
Maywood and Franston, Ill*

**Contemporary medical management of stable angina pectoris 775**

*H Dirk Soiman MD and Rene A Longou MD  
New Haven Conn*

**Clinical pathologic conference**

**Fundamentals of clinical cardiology**

A reminder  
**LANOXIN<sup>®</sup>**  
(digoxin)



Manufactured by  
Lanoxin, Inc.  
New York, N.Y.

|   |  |
|---|--|
| Appraisal and reappraisal<br>of cardiac therapy | Management of shock following acute myocardial infarction Part<br>II Mechanical circulatory assistance 789<br><i>Leslie A Kohn MD New York N Y</i>   |
| Special report                                  | Definition of terms related to cardiac rhythm 796<br><i>WHO/ISC Task Force Utrecht The Netherlands and New York N Y</i>  |
| Annotations                                     | Fine flutterings of the aortic valve as demonstrated by aortic valve<br>echocardiograms 807<br><i>Eduard R Pinto MD Prabodh M Damant MD Cora N Sternberg MD and<br/>A James Liedtke Hershey Pa</i><br>Appropriate therapy of hypertension in the elderly 809<br><i>D T C Barlow MB BS FRCGP Barnstaple England</i><br>Pulmonary vascular effects of verapamil 810<br><i>Allan Davidson MD Ian McMurtry PhD and J T Reeves MD Denver Colo</i><br>Of why the two heart pumps are anatomically united to form one<br>heart 811<br><i>George E Burch MD New Orleans La</i> |
| Letters to<br>the Editor                        | Parasystole and re entry 812<br><i>Shinji Kinoshita MD Sapporo Japan</i><br>Reply 813<br><i>Paul R Lightfoot MD Fontana Calif</i><br>More on effectiveness of the CCU 813<br><i>PierFilippo Fazzini Francesco Marchi and Paolo Pucci Florence Italy</i><br>MLAP LVEDP and left ventricular dysfunction 814<br><i>Ali Haddad MD and Vassil A Prokhor MD Buffalo N Y</i><br>Reply 814<br><i>Nicholas T Kouchoukos MD and Robert B Karp MD Birmingham Ala</i>   |
| Book reviews                                    | Book reviews 815   |
| Books received                                  | Books received 816   |
| Announcements                                   | Announcements 816  |
| Index   | Author index 819<br>Subject index 825<br><br>(Information for authors on page 13)  |



## No Matter How You Look At It...

With the experience of over 155,000 aortic and mitral valve replacements annually, the Björk & Shiley Cardiac Valve Company continues to be the choice of cardiac surgeons for aortic and mitral valvular replacement. Completely aortic root or leaflet only, supported by a wealth of excellent clinical evidence, the Björk & Shiley aortic valve preserves the structural integrity of the aortic chamber. The Björk & Shiley prosthetic aortic valve is about the size of a golf ball. If your procedure requires aortic root replacement, you would use the Björk & Shiley aortic valve.

**Björk & Shiley**

|   |   |
|---|---|
| Appraisal and reappraisal<br>of cardiac therapy | Management of shock following acute myocardial infarction Part<br>II Mechanical circulatory assistance 789<br><i>Leslie A Kuhn MD New York N Y</i>  |
| Special report                                  | Definition of terms related to cardiac rhythm 796<br><i>WHO/ISC Task Force Utrecht The Netherlands and New York N Y</i>   |
| Annotations                                     | Fine flutterings of the aortic valve as demonstrated by aortic valve<br>echocardiograms 807<br><i>Eduard R Pinto MD Prabodh V Damani MD Cora N Sternberg MD and<br/>A James Liedtke Hershey Pa</i><br>Appropriate therapy of hypertension in the elderly 809<br><i>D T C Barlow MB BS FRCPG Barnstaple England</i><br>Pulmonary vascular effects of verapamil 810<br><i>Allan Davidson MD Ivan McMurtry PhD and J T Reeves MD Denver Colo</i><br>Of why the two heart pumps are anatomically united to form one<br>heart 811<br><i>George E Burch MD New Orleans La</i> |
| Letters to<br>the Editor                        | Parasystole and re entry 812<br><i>Shunji Kinoshita MD Sapporo Japan</i><br>Reply 813<br><i>Paul R Lightfoot MD Fontana Calif</i><br>More on effectiveness of the CCU 813<br><i>PierFilippo Fazzini Francesco Marchi and Paolo Pucci Florence Italy</i><br>MLAP LVEDP and left ventricular dysfunction 814<br><i>Ali Haddad MD and Vassil A Prokhor MD Buffalo N Y</i><br>Reply 814<br><i>Nicholas T Kouchoukos MD and Robert B Karp MD Birmingham Ala</i>  |
| Book reviews                                    | Book reviews 815  |
| Books received                                  | Books received 816  |
| Announcements                                   | Announcements 816   |
| Index   | Author index 819<br>Subject index 825<br><br>(Information for authors on page 13)   |





## Editorial

### The comeback of hydralazine

Jan Koch Weser M.D.  
Strasbourg France

In most patients with chronic primary hypertension abnormally high peripheral vascular resistance is the proximate cause of elevated arterial pressure.<sup>1-3</sup> Their cardiac output is generally within the normal range although it may have been elevated in the early stages of their disease and may become subnormal should cardiac failure supervene. The arterial pressure of hypertensive patients can be lowered either by decreasing cardiac output or by lowering total peripheral resistance but the former approach adds a second hemodynamic abnormality to compensate for the existing disturbance. The circulation of the chronic hypertensive patient whose arterial pressure has been normalized by depressing cardiac output is doubly abnormal: vascular resistance remains excessive and cardiac output is now abnormally low. This situation is inescapably associated with decreased tissue perfusion quite probably including heart, brain and kidneys, hardly a desirable long term hemodynamic goal. It would seem preferable to return the excessive total peripheral resistance to normal. That is to say, drug therapy of established primary hypertension should dilate arterioles.

With the exception of propranolol all antihypertensive drugs are vasodilators. However most of them act by decreasing the sympathetic stimulation of veins, heart and arterioles. Thereby they tend to decrease both cardiac output and peripheral resistance. The relative

hypotensive contribution of these two mechanisms varies greatly. It depends on a host of factors including the specific drug and its dose, the duration of therapy, the patient's hemodynamic characteristics prior to therapy, the state of his vasculature and his body position. Nevertheless in antihypertensively effective doses any sympathodepressant—regardless of whether it acts by decreasing vasomotor outflow by ganglionic blockade, by interfering with norepinephrine release from sympathetic nerve endings or by antagonism at adrenergic receptors—cannot fail to depress cardiac output when ever adrenergic stimulation of capacitance vessels and heart is normally important in maintaining it. This is always true in the upright posture and during exercise but in many hypertensive patients it applies even during supine rest.

If the desired hemodynamic effect in antihypertensive therapy is dilation of abnormally constricted arterioles why not choose a drug that relaxes arteriolar smooth muscle specifically without affecting the heart or the venous system? Why not pick a compound that acts directly on smooth muscle so that its efficacy will be independent of the vasoconstrictor mechanisms operating? Hydralazine is such a drug and having become available 20 years ago is one of the oldest antihypertensives. However it is only now reaching its full potential.

A bit of luck marked the introduction of hydralazine into clinical therapy. The drug was launched for treatment of hypertension rather than being thrown into the quixotic attack on peripheral arterial insufficiency caused by structural arterial changes that has given vasodilators a bad name. It was soon found that hydralazine

From the Centre de Recherche Merrell International 1, Strasbourg France

Received for publication Apr. 13, 1977

Reprint request: J. n. Koch Weser M.D. Centre de Recherche Merrell International, Strasbourg Cedex 67046 France



85



## Editorial

### The comeback of hydralazine

Jan Koch Weser MD

Strasbourg France

In most patients with chronic primary hypertension abnormally high peripheral vascular resistance is the proximate cause of elevated arterial pressure.<sup>1</sup> Their cardiac output is generally within the normal range although it may have been elevated in the early stages of their disease and may become subnormal should cardiac failure supervene. The arterial pressure of hypertensive patients can be lowered either by decreasing cardiac output or by lowering total peripheral resistance but the former approach adds a second hemodynamic abnormality to compensate for the existing disturbance. The circulation of the chronic hypertensive patient whose arterial pressure has been normalized by depressing cardiac output is doubly abnormal: vascular resistance remains excessive and cardiac output is now abnormally low. This situation is inescapably associated with decreased tissue perfusion quite probably including heart, brain and kidneys, hardly a desirable long term hemodynamic goal. It would seem preferable to return the excessive total peripheral resistance to normal.<sup>2</sup> That is to say drug therapy of established primary hypertension should dilate arterioles.

With the exception of propranolol all antihypertensive drugs are vasodilators. However most of them act by decreasing the sympathetic stimulation of veins, heart and arterioles. Thereby they tend to decrease both cardiac output and peripheral resistance. The relative

hypotensive contribution of these two mechanisms varies greatly. It depends on a host of factors including the specific drug and its dose, the duration of therapy, the patient's hemodynamic characteristics prior to therapy, the state of his vasculature and his body position. Nevertheless in antihypertensively effective doses any sympathodepressant—regardless of whether it acts by decreasing vasomotor outflow by ganglionic blockade, by interfering with norepinephrine release from sympathetic nerve endings or by antagonism at adrenergic receptors—cannot fail to depress cardiac output when ever adrenergic stimulation of capacitance vessels and heart is normally important in maintaining it. This is always true in the upright posture and during exercise but in many hypertensive patients it applies even during supine rest.

If the desired hemodynamic effect in antihypertensive therapy is dilation of abnormally constricted arterioles, why not choose a drug that relaxes arteriolar smooth muscle specifically without affecting the heart or the venous system? Why not pick a compound that acts directly on smooth muscle so that its efficacy will be independent of the vasoconstrictor mechanisms operating? Hydralazine is such a drug and having become available 25 years ago is one of the oldest antihypertensives. However it is only now reaching its full potential.<sup>3</sup>

A bit of luck marked the introduction of hydralazine into clinical therapy. The drug was launched for treatment of hypertension rather than being thrown into the quixotic attack on peripheral arterial insufficiency caused by structural arterial changes that has given vasodilators a bad name. It was soon found that hydralazine

From the Centre de Recherche Merrell International, Strasbourg, France.

Received for publication April 13, 1977.

Reprint request: J. Koch Weser MD, Centre de Recherche Merrell International, Strasbourg Cedex 67044, France.



dosages of up to 300 mg should only be administered to fast acetylators

Other untoward effects of hydralazine such as headache, dizziness, flushing, nasal congestion, palpitations, increases in cardiac work and oxygen consumption, anginal attacks and electrocardiographic changes of myocardial ischemia are all related to the vasodilator action of the drug or to the reflex responses to that action. They are no problem when low doses of hydralazine are administered to patients treated with propranolol. Even hypertensive patients with limited coronary reserve and with symptoms or signs of myocardial ischemia can be successfully treated with this combination of drugs.<sup>4, 5</sup>

One drawback of hydralazine as antihypertensive therapy has been the practice of administering 4 doses per day. This dosage schedule was presumed necessary because of the two to five hour half life of hydralazine in the plasma of most subjects. However, the drug has special affinity for arterial smooth muscle and persists longer there than in the blood. The half time of the antihypertensive action of hydralazine is far longer than the plasma elimination half life. Not surprisingly, two daily doses of hydralazine are quite sufficient for good blood pressure control during chronic therapy. Happily, the same has also been shown for propranolol.

Treatment of hypertension with direct and specifically acting vasodilator drugs is now receiving the attention it deserves. More than a dozen such drugs are under study for this purpose. Some of them may ultimately turn out

to be more effective and safer than hydralazine. For the present, hydralazine is one of the most valuable antihypertensive agents and the first one that has come back.

#### REFERENCES

1. Fries E D. Hemodynamics of hypertension. *Physiol Rev* 40:27, 1960.
2. Frohlich E D, Tarazi, R C and Dustan H P. Re-examination of the hemodynamics of hypertension. *Ann J Med Sci* 257:9, 1969.
3. Koch-Weser J. Correlation of pathophysiology and pharmacotherapy in primary hypertension. *Am J Cardiol* 32:499, 1973.
4. Koch-Weser J. Vasodilator drugs in the treatment of hypertension. *Arch Intern Med* 133:1017, 1974.
5. Koch-Weser J. Modern approaches to the treatment of hypertension. In: Gouva W A, Tognoni G, and van der Kleijn E, editors. *Clinical pharmacology and pharmacology*. Amsterdam, 1976. North Holland Publishing Company, p. 111.
6. Koch-Weser J. Hydralazine. *N Engl J Med* 295:320, 1976.
7. Fries E D, Rose J C, Higgins T F, Finnerty F A, Kelley R T and Iartenope E A. The hemodynamic effects of hypotensive drugs in man. IV. Hydralazine. *Circulation* 8:199, 1973.
8. Zaccari R, Gilmore E, and Koch-Weser J. Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. *N Engl J Med* 286:617, 1972.
9. Zaccari R and Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 13:470, 1972.
10. Strandberg L, Boman G, Hassa L and Sjöqvist F. Acetylator phenotype in patients with hydralazine-induced lupoid syndrome. *Acta Med Scand* 200:367, 1976.
11. O'Malley K, Segal J L, Israeli Z H, Boles M, McVay J L and Dayton P G. Duration of hydralazine action in hypertension. *Clin Pharmacol Ther* 18:581, 1975.

1

•

•

1

•

•

1

1

1

1

1

4

5

1

1

•

1



different subjects is meaningless. Consequently control readings were given an arbitrary value of 100 and the readings during isometric and dynamic exercise were expressed as a percentage of the control value immediately preceding the exercise. Arterial blood pressure was measured by sphygmomanometry before during and after sustained isometric handgrip exercise the cuff being applied to the non exercising arm.

For the isometric exercise studies each subject's maximum grip strength (MVC) was ascertained and the dynamometer was set at 30 per cent of this value. The standard strain gauge dynamometer is similar to that used in previous studies. The original indicating mechanism is replaced by a miniature linear displacement transducer whose electrical output is measured on a voltmeter scale calibrated from 0 to 50 kg. A 50 kg thrust produces a 5 mm displacement.

After a 30 minute rest period control values for heart rate, blood pressure and  $S_1$  amplitude were obtained and the subject was then instructed to maintain 10 per cent MVC for three minutes using his right hand. Further readings were taken during the final 30 seconds of handgrip and again four minutes later. Care was taken to ensure that the subjects did not perform a Valsalva maneuver as has been emphasized previously. This level of muscular effort has consistently been shown to elicit significant increases in heart rate and blood pressure.

After resting for 20 minutes the control observations were repeated following which the subjects exercised in the erect posture on a bicycle ergometer at an initial load of 600 kilopond meters (k.p.m.) while maintaining a pedal speed of 50 to 60 rpm. The load was increased by 100 k.p.m. every minute until a heart rate of 170 beats per minute was attained. The post exercise recordings of electrocardiogram and phonocardiogram were made one minute after the completion of exercise and again 20 minutes later. This level of dynamic exercise has been shown to approximate to 70 per cent maximal oxygen consumption.

Thirty minutes after the end of exercise a control reading was taken and propranolol (Intral) was then administered intravenously in a dose of 0.2 mg per kg of body weight over a period of five minutes in a total volume of 30 ml. This dose has been shown to produce a potent



Fig 1 The ultra low frequency phonocardiogram (lower tracing) Above electrocardiogram

beta adrenergic blocking effect. Five minutes after completion of the injection the above sequence of maneuvers and recordings was repeated. Although under these circumstances it is clear that a steady state is not achieved the resting values for the amplitude of  $S_1$  before isometric and dynamic exercise following administration of the drug were virtually identical suggesting that at rest the effects of the drug were comparable at these times.

The results for the individual are expressed as the mean value  $\pm$  one standard deviation and for the group as a whole as the mean value  $\pm$  one standard error of the mean. The significance levels of the hemodynamic responses to the various interventions and comparisons of these responses before and after propranolol were calculated by Student's paired  $t$  test using a Burroughs desk top computer (C 3660) following log transformation of the data.

## Results

Fig 1 illustrates the configuration of the ultra low frequency phonocardiogram. The results are summarized in Tables I to III and Figs 2 and 3.

**A Effects of dynamic exercise.** One minute after the cessation of bicycle exercise group mean heart rate was 104 beats per minute compared with a control value of 66 beats per minute ( $p < 0.001$ ) (Table I). On average the  $S_1$  amplitude increased by  $107 \pm 27$  per cent ( $p < 0.001$ ) (Table I, Figs 2 and 3).

After propranolol dynamic exercise increased group mean heart rate from 64 to 79 beats per minute ( $p < 0.02$ ) (Table I), a change which was significantly less than that occurring during exercise before the administration of the drug ( $p$





Table I Effects of dynamic exercise

| Subject | Mode     | Before propranolol              |                 | Mode     | After propranolol               |                 |
|---------|----------|---------------------------------|-----------------|----------|---------------------------------|-----------------|
|         |          | Heart Rate (min <sup>-1</sup> ) | S amplitude (°) |          | Heart rate (min <sup>-1</sup> ) | S amplitude (%) |
| 1       | Control  | 83                              | 100(9)          | Control  | 73                              | 100(12)         |
|         | Exercise | 104                             | 99(11)          | Exercise | 91                              | 144(16)         |
|         | Control  | 61                              | 100(9)          | Control  | 67                              | 100(17)         |
| 3       | Exercise | 109                             | 285(11)         | Exercise | 86                              | 149(74)         |
|         | Control  | 62                              | 100(6)          | Control  | 63                              | 100(9)          |
|         | Exercise | 91                              | 148(70)         | Exercise | 84                              | 110(22)         |
| 4       | Control  | 67                              | 100(15)         | Control  | 60                              | 100(14)         |
|         | Exercise | 115                             | 118(11)         | Exercise | 80                              | 124(9)          |
|         | Control  | 58                              | 100(12)         | Control  | 58                              | 100(20)         |
| 5       | Exercise | 66                              | 140(9)          | Exercise | 49                              | 172(12)         |
|         | Control  | 71                              | 100(15)         | Control  | 63                              | 100(10)         |
| 6       | Exercise | 139                             | 251(14)         | Exercise | 83                              | 130(11)         |
|         | Control  | 66(4)                           | 100             | Control  | 64(2)                           | 100             |
| Group   | Exercise | 104(10)                         | 90(20)          | Exercise | 79(6)                           | 143(11)         |
|         | Change   | +38(9)                          | +10(10)         | Change   | +15(4)                          | +43(9)          |
|         | p        | < 0.001                         | < 0.001         | p        | < 0.02                          | < 0.005         |

Figures in parentheses represent standard error of the mean for the group data and standard deviation for the individual data.

the average systolic blood pressure increased from 107 to 120 mm Hg during handgrip ( $p < 0.05$ ) (Table II) and average diastolic blood pressure increased from 75 to 93 mm Hg ( $p < 0.001$ ) (Table II). These changes were not significantly different from the changes which occurred during handgrip before the administration of propranolol ( $p > 0.10$  for both) (Fig. 2). After propranolol there was no significant change in the amplitude of S during handgrip ( $p > 0.98$ ) (Table II, Fig. 2). This response was also not significantly different from that observed before the drug was given ( $p > 0.10$ ) (Fig. 2).

**Effects of propranolol at rest.** Propranolol produced a significant reduction in mean resting heart rate from 76 to 67 beats per minute ( $p < 0.005$ ) (Table III). There was no significant change in systolic ( $p > 0.20$ ) or diastolic ( $p > 0.60$ ) blood pressure for the group as a whole (Table III). At rest propranolol reduced the amplitude of S by  $20 \pm 6$  per cent ( $p < 0.01$ ) (Table III, Fig. 2).

### Discussion

The traditional view that the first heart sound (S<sub>1</sub>) is caused by atrioventricular valve closure has been questioned in recent years largely because of the observation that the initial vibra-

tions of S do not begin until after these valves are completely closed.<sup>1</sup> Several investigators have suggested that the vibrations which are detected at the precordium as heart sounds are in fact generated by those intracardiac forces which are responsible for accelerating and decelerating the heart and great vessels and the blood contained within them.<sup>2,3,11</sup> Indeed a close temporal relationship has been demonstrated between events in the phonocardiogram and the acceleration and deceleration of blood flow in the central aorta.<sup>12</sup> On the basis of these results and theoretical considerations it appears that the production of heart sounds is closely related to the phenomenon of acceleration in the central circulation.

In the present study the ultra low frequency phonocardiogram was recorded in the form of the precordial acceleration tracing whose configuration has been described by previous workers.<sup>1,13</sup> This tracing responds to instantaneous changes in the acceleration of the precordium throughout the cardiac cycle and closely resembles the pattern of the second time derivatives of the aortic pressure pulse and of precordial displacement records.<sup>2</sup> The precordial accelerocardiogram possesses some important practical advantages over more familiar techniques for



Table 1 Effects of dynamic exercise

| Subject | Mode     | Before propranolol              |                 | Mode     | After propranolol               |                 |
|---------|----------|---------------------------------|-----------------|----------|---------------------------------|-----------------|
|         |          | Heart Rate (min <sup>-1</sup> ) | S amplitude (°) |          | Heart rate (min <sup>-1</sup> ) | S amplitude (°) |
| 1       | Control  | 83                              | 100( 9)         | Control  | 73                              | 100(12)         |
|         | Exercise | 104                             | 2° (31)         | Exercise | 91                              | 14(16)          |
| 2       | Control  | 61                              | 100( 9)         | Control  | 66                              | 100(1 )         |
|         | Exercise | 109                             | 28(11)          | Exercise | 86                              | 1°(24)          |
| 3       | Control  | 6°                              | 100( 10)        | Control  | 63                              | 100( 9)         |
|         | Exercise | 91                              | 14°(10)         | Exercise | 84                              | 110(??)         |
| 4       | Control  | 6°                              | 100(15)         | Control  | 60                              | 100(14)         |
|         | Exercise | 115                             | 178(11)         | Exercise | 80                              | 1°4( 9)         |
| 5       | Control  | 59                              | 100(1°)         | Control  | 56                              | 100(°0)         |
|         | Exercise | 66                              | 140( 9)         | Exercise | 49                              | 1 2(1°)         |
| II      | Control  | 71                              | 100(15)         | Control  | 63                              | 100(10)         |
|         | Exercise | 139                             | 261(14)         | Exercise | 83                              | 130(11)         |
| Group   | Control  | 66( 4)                          | 100             | Control  | 64(2)                           | 100             |
|         | Exercise | 104(10)                         | °0°(20)         | Exercise | °9(6)                           | 143(11)         |
|         | Change   | +38( 9)                         | +10 (27)        | Change   | +15(4)                          | +43( 9)         |
|         | p        | < 0.001                         | < 0.001         | p        | < 0.0°                          | < 0.003         |

Fig. in parentheses represent 1 standard error of the mean value for the group and 1 standard deviation for the individual data

the average systolic blood pressure increased from 107 to 120 mm Hg during handgrip ( $p < 0.05$ ) (Table II) and average diastolic blood pressure increased from 73 to 93 mm Hg ( $p < 0.001$ ) (Table II). These changes were not significantly different from the changes which occurred during handgrip before the administration of propranolol ( $p > 0.10$  for both) (Fig. 2). After propranolol there was no significant change in the amplitude of S during handgrip ( $p > 0.98$ ) (Table II, Fig. 2). This response was also not significantly different from that observed before the drug was given ( $p > 0.10$ ) (Fig. 2).

**C Effects of propranolol at rest.** Propranolol produced a significant reduction in mean resting heart rate from 76 to 67 beats per minute ( $p < 0.001$ ) (Table III). There was no significant change in systolic ( $p > 0.20$ ) or diastolic ( $p > 0.60$ ) blood pressure for the group as a whole (Table III). At rest propranolol reduced the amplitude of S by  $20 \pm 8$  per cent ( $p < 0.01$ ) (Table III, Fig. 2).

### Discussion

The traditional view that the first heart sound (S<sub>1</sub>) is caused by atrioventricular valve closure has been questioned in recent years largely because of the observation that the initial vibra-

tions of S<sub>1</sub> do not begin until after these valves are completely closed.<sup>2-4</sup> Several investigators have suggested that the vibrations which are detected at the precordium as heart sounds are in fact generated by those intracardiac forces which are responsible for accelerating and decelerating the heart and great vessels and the blood contained within them.<sup>2-22</sup> Indeed a close temporal relationship has been demonstrated between events in the phonocardiogram and the acceleration and deceleration of blood flow in the central aorta.<sup>1</sup> On the basis of these results and theoretical considerations it appears that the production of heart sounds is closely related to the phenomenon of acceleration in the central circulation.

In the present study the ultra low frequency phonocardiogram was recorded in the form of the precordial acceleration tracing whose configuration has been described by previous workers.<sup>1-13</sup> This tracing responds to instantaneous changes in the acceleration of the precordium throughout the cardiac cycle and closely resembles the pattern of the second time derivatives of the aortic pressure pulse<sup>2</sup> and of precordial displacement records.<sup>2</sup> The precordial accelerocardiogram possesses some important practical advantages over more familiar techniques for

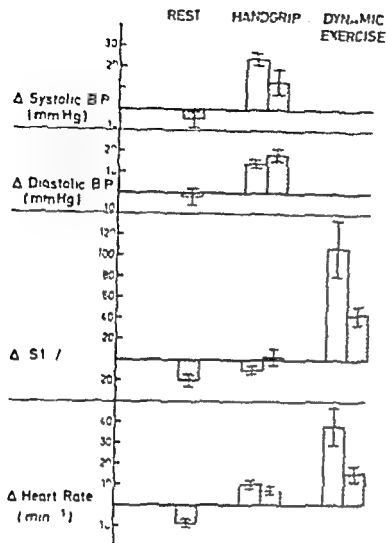


Fig. 2 Hemodynamic effects of handgrip dynamic exercise and propranolol. Left hand column represents effects of propranolol at rest, center column the effects of handgrip and right hand column the effects of dynamic exercise. Blacks represent the group mean change in blood pressure, heart rate and S1 amplitude and bars represent the standard error of the mean. Clear blacks represent the effects of exercise before propranolol and shaded blacks represent the changes after propranolol.

$< 0.001$ ) (Figs. 2 and 3). After the drug dynamic exercise increased the amplitude of S1 by  $43 \pm 9$  per cent ( $p < 0.001$ ) (Table II) which again was significantly less than the increase observed before the drug was administered ( $p < 0.02$ ) (Figs. 2 and 3).

For the group as a whole there was equivalent suppression of the chronotropic and phonocardiographic responses to dynamic exercise by propranolol (Fig. 3).

**B. Effects of handgrip.** Handgrip increased group mean heart rate from 69 to 79 beats per minute ( $p < 0.001$ ) (Table II). Group mean systolic blood pressure increased from 114 to 120 mm Hg ( $p < 0.001$ ) and diastolic pressure

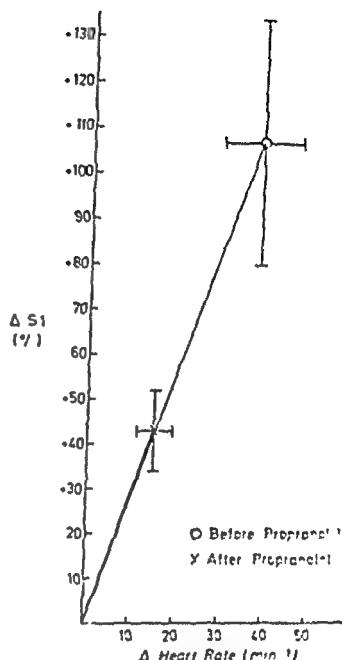


Fig. 3 Effect of propranolol on the response to dynamic exercise. Circle and cross represent group mean values and bars represent standard error of the mean.

increased from 77 to 91 mm Hg ( $p < 0.001$ ) (Table II). The S1 amplitude decreased on average by  $10 \pm 4$  per cent a change which was just statistically significant ( $p = 0.01$ ) (Table II, Fig. 2). Although the numbers were small there was no correlation between the individual changes in the amplitude of S1 or the changes in heart rate and blood pressure.

After propranolol handgrip increased group mean heart rate from 77 to 84 beats per minute ( $p < 0.001$ ) (Table II) which was not significantly different from the increase observed before the drug ( $p = 0.10$ ) (Fig. 2). After the drug

supine position (Table III Fig 2) which confirms previous observations made in animals.<sup>1</sup> Interestingly the drug has also been shown to decrease peak aortic acceleration in dogs.<sup>2</sup> A depressant effect of propranolol on the normal human heart has been demonstrated previously by Parker and associates<sup>1</sup> in a small group of resting subjects. Whether this observation reflects the presence of significant cardiac sympathetic tone at rest or a depressant effect of propranolol independent of its beta adrenergic blocking properties remains conjectural.

Isometric handgrip exercise has been employed in many cardiac laboratories as a stress test for the evaluation of left ventricular performance.<sup>3</sup> Previous workers have shown that the normal left ventricular response to isometric exercise includes an increase in contractile state.<sup>4,5</sup> In most studies this conclusion has been reached by the construction of ventricular function curves,<sup>6</sup> but these are thought to be unreliable in defining left ventricular contractile state in situations in which aortic pressure is changing as it is during isometric handgrip. More convincing evidence of an increase in left ventricular contractility during handgrip is the observation that the isovolumetric indices of contractility are increased.<sup>7</sup> This increase in contractile state was not reflected in an increase in the amplitude of S (Table II). Our failure to show an increase in S amplitude was certainly not due to an inadequate level of isometric exercise since the magnitudes of the tachycardia and pressor response observed in the present study were similar to those reported previously.<sup>8</sup> Acute increases in blood pressure induced by the infusion of vasoconstrictor drugs have previously been shown to reduce the intensity of the high frequency components of S which might suggest that the effect of the pressor response on the amplitude of S outweighs and obscures any cardiac inotropic effects of handgrip. However sustained increases in peripheral vascular resistance have been shown not to influence either the amplitude of the low frequency components of S or its hemodynamic equivalent peak aortic acceleration.<sup>9</sup> Furthermore we have previously shown that those cardiac patients in whom left ventricular function is well maintained respond to handgrip with an increase in S amplitude despite increases in blood pressure compa-

Table III Effects of propranolol at rest

| Subject | Mode        | Heart rate (min) | Systolic BP (mm Hg) | Diastolic BP (mm Hg) | S amplitude (%) |
|---------|-------------|------------------|---------------------|----------------------|-----------------|
| 1       | Control     | 85               | 118                 | 84                   | 100(12)         |
|         | Propranolol | 78               | 98                  | 60                   | 83(12)          |
| 2       | Control     | 80               | 130                 | 80                   | 100(10)         |
|         | Propranolol | 69               | 125                 | 80                   | 59(14)          |
| 3       | Control     | 84               | 90                  | 55                   | 100(9)          |
|         | Propranolol | 66               | 90                  | 60                   | 70(12)          |
| 4       | Control     | 73               | 118                 | 70                   | 100(11)         |
|         | Propranolol | 64               | 110                 | 70                   | 95(15)          |
| 5       | Control     | 60               | 100                 | 80                   | 100(9)          |
|         | Propranolol | 60               | 110                 | 80                   | 75(10)          |
| 6       | Control     | 79               | 110                 | 85                   | 100(8)          |
|         | Propranolol | 67               | 110                 | 80                   | 93(7)           |
| Group   | Control     | 76(4)            | 117(6)              | 77(5)                | 100             |
|         | Propranolol | 67(9)            | 107(5)              | 70(5)                | 80(5)           |
|         | Change      | -9(7)            | -10(4)              | -7(4)                | -20(6)          |
|         | p           | < 0.005          | > 0.20              | > 0.60               | < 0.01          |
|         |             |                  |                     | NS                   |                 |

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

table with those occurring in normal subjects.<sup>10</sup> This suggests that the rise in blood pressure per se is not responsible for the decline in S amplitude in these young normal subjects. Direct measurements of peak aortic acceleration during handgrip may help to clarify the situation.

The different effects of beta adrenergic blockade on the cardiac responses to isometric and dynamic exercise observed here lends support to the view that in contrast to dynamic exercise beta adrenergic activation contributes little to the adaptation to the stress of isometric handgrip. In fact no significant change could be seen in the response to handgrip after propranolol as regards heart rate blood pressure or S amplitude (Fig 2). Previous studies involving the use of beta adrenergic blocking drugs have shown that the tachycardia associated with sustained isometric handgrip is relatively independent of the beta adrenergic nervous system in normal subjects.<sup>11</sup> Beta blockade has also been shown not to impair the pressor response to handgrip but under these circumstances an increase in peripheral vascular resistance makes a greater contribution and an increase in cardiac output a lesser one to the rise in blood pressure.<sup>12</sup> Furthermore plasma catecholamine levels do not increase impressively during sustained handgrip in young normal



supine position (Table III Fig 2) which confirms previous observations made in animals.<sup>2, 22</sup> Interestingly the drug has also been shown to decrease peak aortic acceleration in dogs.<sup>2, 23</sup> A depressant effect of propranolol on the normal human heart has been demonstrated previously by Parker and associates<sup>24</sup> in a small group of resting subjects. Whether this observation reflects the presence of significant cardiac sympathetic tone at rest or a depressant effect of propranolol independent of its beta adrenergic blocking properties remains conjectural.

Isometric handgrip exercise has been employed in many cardiac laboratories as a stress test for the evaluation of left ventricular performance.<sup>2, 25</sup> Previous workers have shown that the normal left ventricular response to isometric exercise includes an increase in contractile state. In most studies this conclusion has been reached by the construction of ventricular function curves<sup>26, 27</sup> but these are thought to be unreliable in defining left ventricular contractile state in situations in which aortic pressure is changing as it is during isometric handgrip. More convincing evidence of an increase in left ventricular contractility during handgrip is the observation that the isovolumetric indices of contractility are increased. This increase in contractile state was not reflected in an increase in the amplitude of S (Table II). Our failure to show an increase in S amplitude was certainly not due to an inadequate level of isometric exercise since the magnitudes of the tachycardia and pressor response observed in the present study were similar to those reported previously.<sup>2, 28</sup> Acute increases in blood pressure induced by the infusion of vasoconstrictor drugs have previously been shown to reduce the intensity of the high frequency components of S which might suggest that the effect of the pressor response on the amplitude of S outweighs and obscures any cardiac inotropic effects of handgrip. However sustained increases in peripheral vascular resistance have been shown not to influence either the amplitude of the low frequency components of S or its hemodynamic equivalent peak aortic acceleration. Furthermore we have previously shown that these cardiac patients in whom left ventricular function is well maintained respond to handgrip with an increase in S amplitude despite increases in blood pressure compa-

Table III Effects of propranolol at rest

| Subject | Mode        | Heart rate (min <sup>-1</sup> ) | Systolic BP (mm Hg) | Diastolic BP (mm Hg) | S amplitude (%) |
|---------|-------------|---------------------------------|---------------------|----------------------|-----------------|
| 1       | Control     | 85                              | 118                 | 84                   | 100(17)         |
|         | Propranolol | 78                              | 98                  | 80                   | 83(12)          |
| 2       | Control     | 85                              | 130                 | 85                   | 100(10)         |
|         | Propranolol | 69                              | 125                 | 85                   | 59(14)          |
| 3       | Control     | 74                              | 90                  | 75                   | 100(9)          |
|         | Propranolol | 66                              | 90                  | 60                   | 51(7)           |
| 4       | Control     | 73                              | 118                 | 70                   | 100(16)         |
|         | Propranolol | 64                              | 110                 | 71                   | 95(15)          |
| 5       | Control     | 60                              | 105                 | 85                   | 100(9)          |
|         | Propranolol | 60                              | 110                 | 90                   | 51(10)          |
| 6       | Control     | 79                              | 110                 | 85                   | 100(8)          |
|         | Propranolol | 67                              | 110                 | 85                   | 93(7)           |
| Group   | Control     | 78(4)                           | 112(6)              | 77(5)                | 100             |
|         | Propranolol | 67(7)                           | 107(5)              | 75(5)                | 80(5)           |
|         | Change      | -9(2)                           | -5(4)               | -2(4)                | -20(6)          |
| p       |             | < 0.005                         | > 0.20              | > 0.60               | < 0.01          |
|         |             |                                 | NS                  | NS                   |                 |

Figures in parentheses represent 1 standard deviation of the mean value for the group data and 1 standard deviation for the individual data.

table with those occurring in normal subjects.<sup>29</sup> This suggests that the rise in blood pressure per se is not responsible for the decline in S amplitude in these young normal subjects. Direct measurements of peak aortic acceleration during handgrip may help to clarify the situation.

The different effects of beta adrenergic blockade on the cardiac responses to isometric and dynamic exercise observed here lends support to the view that in contrast to dynamic exercise beta adrenergic activation contributes little to the adaptation to the stress of isometric handgrip. In fact no significant change could be seen in the response to handgrip after propranolol as regards heart rate, blood pressure or S amplitude (Fig 2). Previous studies involving the use of beta adrenergic blocking drugs have shown that the tachycardia associated with sustained isometric handgrip is relatively independent of the beta adrenergic nervous system in normal subjects.<sup>30</sup> Beta blockade has also been shown not to impair the pressor response to handgrip but under these circumstances an increase in peripheral vascular resistance makes a greater contribution and an increase in cardiac output a lesser one to the rise in blood pressure. Furthermore plasma catecholamine levels do not increase impressively during sustained handgrip in young normal





- sympathetic blockade on heart rate and cardiac function in man. *Am J Cardiol* 18:46 1966
- 19 Di Bartolo G, Nunez Dey D, Muesen G, MacCanon D M and Luvada A A. Hemodynamic correlates of the first heart sound. *Am J Physiol* 201:888 1961
  - 20 Luvada A A, MacCanon D M, Coleman B and Feigen L P. New studies on the first heart sound. *Am J Cardiol* 23:140 1961
  - 21 Luvada A A, MacCanon D M, Kumar S and Feigen L P. Changing views on the mechanism of the first and second heart sound. *Am Heart J* 88:503 1964
  - 22 van Bogaert A. New concept on the mechanism of the first heart sound. *Am J Cardiol* 18:93 1966
  - 23 Hermine T E, Barnett G O and Dexter L. Relation ship of heart sounds to acceleration of blood flow. *Circ Res* 18:333 1966
  - 24 Hew F F, Lickering D, Sleight P and Stott F D. "Fixe" cardiography: Accelerometer applications to phonocardiography and displacement cardiography in childhood. *Br Heart J* 33: 07 1961
  - 25 Reuben B R and Little W A. Precordial accelerometry and indirect assessment of left ventricular performance. *Eur J Clin Invest* 3:34 1973
  - 26 Ross L M and Kaplan M. Experimental studies on the effect of some cardiovascular drugs on the precordial acceleration tracing. Part II. Irreversible changes. *Exp Med Surg* 7:133 1969
  - 27 Chung D C W, Chamberlain J H and Seed R C F L. The effect of hemodynamic changes on maximum blood flow acceleration at the aortic root in the anaesthetized open-chest dog. *Cardiovasc Res* 8:365 1974
  - 28 Noble M I M, Trenchard D and Gu A. Left ventricular ejection in conscious dogs. I. Measurement and significance of the maximum acceleration of blood from the left ventricle in the dog. *Circ Res* 19:139 1966
  - 29 Nutter D O, Noble R J and Hurst V W. Peak aortic flow and acceleration as indices of ventricular performance in the dog. *J Lab Clin Med* 77:307 1961
  - 30 Epstein S F, Robinson B F, Kahler R L and Braunwald E. Effects of beta adrenergic blockade on the cardiac response to maximal and sub maximal exercise in man. *J Clin Invest* 44:1445 1969
  - 31 Sonnenblick F H, Braunwald E, Williams J F and Glick G. Effects of exercise on myocardial force velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity and ventricular dimensions. *J Clin Invest* 44:905 1965
  - 32 Parker J O, West R O and Di Giampa S. Hemodynamic effects of propranolol in coronary heart disease. *Am J Cardiol* 21:11 1968
  - 33 Sonnenblick E H, Farmley W W, Urschel C W and Brutsaert D L. Ventricular function: evaluation of myocardial contractility in health and disease. *Prog Cardiovasc Dis* 12:449 1970
  - 34 Donald K W, Lind A R, McNicol G W, Humphreys P W, Taylor M H and Staunton H P. Cardiovascular responses to sustained (static) contractions. *Circ Res* 20 (Suppl 1):15 1967
  - 35 McDonald H H, Sapru R P, Taylor S H, and Donald K W. Effects of intravenous propranolol on the systemic circulatory response to sustained handgrip. *Am J Cardiol* 18:333 1966
  - 36 Hume L, Irving J B, Katchin A H and Reuben S R. Effects of sustained isometric handgrip on precordial accelerocardiogram in normal subjects and in patients with heart disease. *Br Heart J* 37:873 1969
  - 37 Martin C E, Shaver J A, Leon M F, Thompson M E, Reddy P M and Leonard J J. Autonomic mechanisms in hemodynamic responses to isometric exercise. *J Clin Invest* 54:104 1964
  - 38 Few J I, Imms F J and Weiner J S. Pituitary adrenal response to static exercise in man. *Clin Sci* 49:901 1975
  - 39 McDermott D J, Stekiel W J, Barboriak J J, Kloth L C and Smith J J. Effect of age on hemodynamic and metabolic response to static exercise. *J Appl Physiol* 37:93 1964
  - 40 Freyschuss U. Elevation of heart rate and blood pressure increase on muscle contraction. *J Appl Physiol* 28:108 1960
  - 41 Seamen R G, Wiley R L, Zechman F W and Goldes J A. Venous reactivity during static exercise (handgrip) in man. *J Appl Physiol* 35:858 1973



Recent studies by Riekkinen and Rautaharju<sup>10</sup> indicate that this level is to be preferred over the fourth intercostal space when the subject is supine. The three orthogonal leads were recorded simultaneously on magnetic tape. Recording techniques and equipment were standardized in all institutions to insure uniformity of results. Methods of data acquisition and details of computational procedures have been described previously.<sup>11</sup> A Control Data Corporation 3200 digital computer was used to obtain 333 different scalar and vectorial measurements for each record comprising practically all parameters previously advocated for analysis of electrocardiograms.

Vectorcardiographic notations followed the recommendations of the American Heart Association Committee on Electrocardiography. Reference frames for spherical coordinates and planar vectors are shown in Fig 2. The left sagittal plane was used. Measurements in scalar  $x$ ,  $y$ ,  $z$  leads included amplitudes and durations of waveforms Q/R and R/S amplitude ratios and the amplitude sum of R + R. The reference level for all QRS measurements was the P-R segment at the beginning of this complex. P and ST segment measurements were referred to the level of the T-P interval.<sup>12</sup>

Instantaneous QRS vectors were determined at 0.01, 0.02, 0.03, and 0.04 second intervals from the onset and in a retrograde fashion from the end of this complex. Planar magnitudes of these vectors were computed from the corresponding scalar components. Instantaneous ST-T vectors were obtained at 0.02, 0.04, and 0.06 second intervals from the J point. To improve comparability of QRS and ST-T vectors in different individuals, these complexes were also time normalized by dividing their total durations into eight equal time segments regardless of the absolute values. The mean amplitudes of vectors in the end of each time segment were used for graphic representation of the total QRS-T complex.

Maximal P, QRS, and T vectors were determined in pace and in the three projection planes. These vectors represent the vectors of the largest magnitude drawn from the origin of the QRS loop (F point). Half area QRS vectors were also calculated in each projection plane. These vectors originate from the F point, bisect the total QRS loop area, and usually lie in close approximation to the true mean spatial QRS vector.

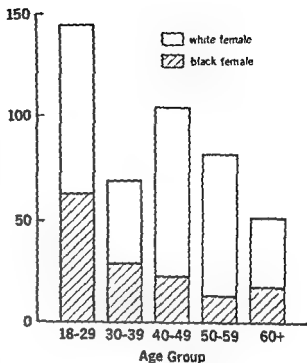


Fig 1 Age and race distributions of 400 normal women. The shaded area in each age group depicts the fraction that was black.

Direction of inscription of the QRS loop in three plane projections was determined using the principle of vector multiplication.<sup>13</sup> Means, standard deviations, and 96 percentile ranges of amplitude items were computed from the total number of measurements available. Mean angles and 96 percentile angular ranges were determined by center of gravity<sup>14</sup> method and by examining in detail histograms of distributions. Ninety six percentile ranges correspond to a mean  $\pm 2$  standard deviations whenever a normal distribution is present. Since most electrocardiographic data exhibit skewed distributions, the use of these ranges instead of standard deviations is a more practical and realistic description of normality.

Statistics from women were compared with those of 510 normal men. Significance of differences between the samples was determined by Kolmogorov-Smirnov's two sample test for amplitudes and by F tests<sup>15</sup> for vector angles.

## Results

Scalar, planar, and spatial measurements are presented in Tables I-V. More emphasis is given to scalar measurements because of their ease of application in daily clinical practice. QRS loop rotations are presented in Table VI. A compar-

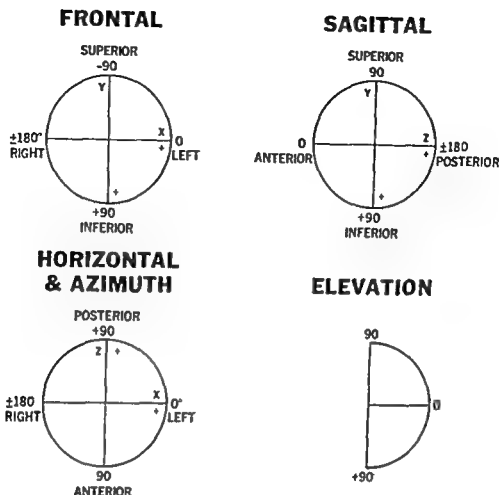


Fig. 2 Reference frames for vector directions and orientations

ison is made between these results and those of 510 normal age matched men<sup>6</sup> and the sex specific limits of clinical importance are summarized in Table VII<sup>6</sup>

**Scalar measurements** Table I represents amplitudes and durations of waveforms in x, y, z leads. Also shown are Q/R and R/S amplitude ratios and the amplitude sum of R + R. The latter measurement was found to be a useful indicator of left ventricular hypertrophy in a previous study of patients with hypertensive cardiovascular disease. Q waves were absent in 47 per cent of the normal records in either Lead x or y. They were also absent in 4 cases (1 per cent) in Lead z, corresponding to the absence of initial R waves in the right precordial leads. S waves occurred more frequently in Lead x (70 per cent) than in Lead y (56 per cent). In addition 2 cases (2 per cent) had also had an S wave in Lead z (corresponding to RR patterns in right precordial leads) with a normal QRS duration.

A list of additional measurements not reported in this communication is available from the authors upon request.

Amplitudes of instantaneous QRS and ST-T vectors are shown in Table II. Time interval appears in Table III.

**Planar and spatial measurements** Planar amplitudes and directions of maximal P, QRS and T as well as half area and instantaneous QRS vectors are shown in Table IV. Spherical coordinates of maximal vectors appear in Table V. It should be noted that planar amplitudes of instantaneous vectors are determined from scalar components of the corresponding leads rather than vector loops. Measurements of these vectors from time markings of the vector loops frequently lead to erroneous results because of difficulties in delineating the closely spaced initial parts of the QRS loop and because of the superimposition of the P and T loop on its early and late portions. Furthermore, the QRS onset frequently differs from one component lead to another, resulting in discrepancies in temporal relationships between corresponding leads and time markings in different plane projections.

Initial and terminal QRS vector angles, particularly in the frontal plane display wide scatter

Table I Measurements of P QRS and T in orthogonal x y z leads

| Item  | x lead                               | y lead                               | z lead   |
|---|--------------------------------------|--------------------------------------|--|
| P amplitude                                 | 0.05 ± 0.02<br>0.02 → 0.09           | 0.09 ± 0.04<br>0.02 → 0.17           | Positive component<br>0.03 ± 0.02<br>0 → 0.08<br>Negative component<br>-0.03 ± 0.02<br>-0.07 → 0 |
| Q amplitude                                 | -0.08 ± 0.06 (237)<br>-0.22 → -0.01  | -0.08 ± 0.05 (238)<br>-0.23 → -0.01  | -0.31 ± 0.17 (446)<br>-0.77 → -0.07  |
| R amplitude                                 | 0.94 ± 0.35<br>0.35 → 1.75           | 0.81 ± 0.33<br>0.27 → 1.50           | 0.68 ± 0.27<br>0.22 → 1.25   |
| S amplitude                                 | -0.17 ± 0.11 (319)<br>-0.47 → -0.01  | -0.17 ± 0.19 (257)<br>-0.52 → -0.01  | -0.19 ± 0.17 (9)<br>-0.60 → -0.04  |
| T amplitude                                 | 0.22 ± 0.10<br>0.05 → 0.44           | 0.16 ± 0.09<br>-0.03 → 0.39          | -0.08 ± 0.10<br>-0.31 → 0.10   |
| Q/R amplitude ratio                         | 0.07 ± 0.04 (237)<br>0.01 → 0.18     | 0.09 ± 0.06 (238)<br>0.01 → 0.22     | 0.54 ± 0.47 (446)<br>0.10 → 1.73   |
| R/S amplitude ratio                         | 11.36 ± 18.00 (319)<br>1.12 → 71.70  | 9.20 ± 13.00 (257)<br>0.64 → 56.00   | 4.00 ± 3.30 (9)<br>0.70 → 17.00  |
| Q duration†                                 | 0.016 ± 0.003 (237)<br>0.010 → 0.024 | 0.017 ± 0.004 (238)<br>0.009 → 0.028 | 0.030 ± 0.008 (446)<br>0.014 → 0.041   |
| R duration                                  | 0.045 ± 0.012<br>0.028 → 0.071       | 0.050 ± 0.014<br>0.028 → 0.081       | 0.048 ± 0.010<br>0.028 → 0.069   |
| S duration                                  | 0.029 ± 0.009 (319)<br>0.019 → 0.048 | 0.028 ± 0.009 (257)<br>0.012 → 0.049 | 0.028 ± 0.009 (9)<br>0.018 → 0.044   |
| R peak time<br>(intrinsicoid<br>deflection) | 0.037 ± 0.005<br>0.028 → 0.048       | 0.039 ± 0.006<br>0.027 → 0.050       | 0.048 ± 0.006<br>0.038 → 0.067   |
| R + R                                       | 1.60 ± 0.4<br>0.87 → 2.50            |                                      |  |

Amplitudes are in millivolts.

† Durations are in seconds.

‡ The mean and standard deviation for each item are shown on the upper line.

§ The second column shows the limits of 95 per cent range.

Figures in parentheses show the actual number of observations. Results in the third column by a number in parentheses were obtained from total series.

throughout 360 degrees. The normal ranges of these angles are therefore too large to be of any practical use. Separation of the loops according to different rotation did not significantly decrease the normal angular ranges. Significant sex differences in angular directions are discussed in detail in later paragraphs.

Direction of inscription of QRS loops in three projection planes is shown in Table VI. A variety of rotations occurred in the frontal plane, but in the sagittal and horizontal planes practically all the loops were inscribed counterclockwise. No clockwise loop was observed in the horizontal plane, and the incidence was less than 2 per cent in the sagittal plane. Figure-of-eight loops (both clockwise then counterclockwise and counterclockwise then clockwise) were extremely rare in the horizontal plane. They occurred infrequently in the sagittal plane and then in the majority of

the cases were inscribed counterclockwise in the initial part.

**Comparison with normal men.** Comparison with normal men shows that statistically significant differences in most scalar and vectorial items exist between both sexes. Many of these differences, however, are of limited practical use because of the large overlap of normal ranges of men and women. In Table VII, therefore, only distinct sex-specific limits which can be easily obtained from scalar and vectorcardiographic plane displays are listed for practical applications.

As seen in this table, the mean spatial magnitude of maximal QRS is 22 per cent (0.38 millivolt) and mean maximal T is 35 per cent (0.16 millivolt) less in women than in men. This difference is reflected in all scalar leads and plane projections. Thus, the upper normal limits of R

**Table II** Scalar amplitudes of initial and terminal instantaneous QRS vectors and point J (P R segment as reference level) and instantaneous ST vectors (T P segment as reference level)

|  | x lead       | y lead       | z lead       |
|--|--------------|--------------|--------------|
| <i>Initial vectors from the onset of QRS</i> |              |              |              |
| 0.01 sec                                     | -0.01 ± 0.03 | 0 ± 0.06     | -0.11 ± 0.06 |
|  | -0.11 → 0.10 | -0.13 → 0.12 | -0.23 → 0.01 |
| 0.02 sec                                     | 0.16 ± 0.16  | 0.10 ± 0.14  | -0.22 ± 0.16 |
|  | -0.13 → 0.56 | -0.13 → 0.45 | -0.51 → 0.14 |
| 0.03 sec                                     | 0.62 ± 0.27  | 0.44 ± 0.26  | -0.13 ± 0.31 |
|  | 0.10 → 1.25  | -0.01 → 1.07 | -0.66 → 0.63 |
| 0.04 sec                                     | 0.77 ± 0.41  | 0.63 ± 0.38  | 0.39 ± 0.36  |
|  | 0 → 1.70     | -0.08 → 1.46 | -0.53 → 1.10 |
| <i>Terminal vectors from the end of QRS</i>  |              |              |              |
| point J                                      | 0.00 ± 0.03  | 0.00 ± 0.03  | 0.01 ± 0.03  |
|  | -0.06 → 0.05 | -0.06 → 0.06 | -0.07 → 0.04 |
| 0.01 sec                                     | -0.01 ± 0.03 | 0 ± 0.08     | 0.09 ± 0.07  |
|  | -0.12 → 0.11 | -0.15 → 0.14 | -0.07 → 0.22 |
| 0.02 sec                                     | -0.03 ± 0.15 | 0 ± 0.17     | 0.31 ± 0.17  |
|  | -0.27 → 0.36 | -0.28 → 0.38 | -0.04 → 0.62 |
| 0.03 sec                                     | 0.19 ± 0.38  | 0.21 ± 0.32  | 0.52 ± 0.26  |
|  | -0.29 → 1.18 | -0.35 → 0.97 | -0.05 → 1.04 |
| 0.04 sec                                     | 0.61 ± 0.48  | 0.53 ± 0.40  | 0.44 ± 0.36  |
|  | -0.25 → 1.61 | -0.29 → 1.32 | -0.31 → 1.16 |
| <i>Instantaneous ST vectors</i>              |              |              |              |
| 0.02 sec after                               | -0.02 ± 0.07 | -0.03 ± 0.04 | -0.01 ± 0.03 |
| point J                                      | -0.10 → 0.06 | -0.12 → 0.07 | -0.09 → 0.07 |
| 0.04 sec after                               | -0.01 ± 0.07 | -0.03 ± 0.03 | -0.02 ± 0.04 |
| point J                                      | -0.09 → 0.07 | -0.12 → 0.07 | -0.09 → 0.03 |
| 0.06 sec after                               | 0 ± 0.08     | -0.02 ± 0.07 | -0.02 ± 0.04 |
| point J                                      | -0.08 → 0.07 | -0.11 → 0.07 | -0.10 → 0.03 |

R<sub>x</sub> and R<sub>y</sub> amplitudes are 11 per cent (0.22 millivolt), 20 per cent (0.40 millivolt) and 30 per cent (0.54 millivolt) less respectively in women than in men. The lower normal limit of R<sub>z</sub> is 30 per cent (0.16 millivolt) and mean T amplitude is 70 per cent (0.20 millivolt) smaller in women. The upper normal limit of maximal QRS in this group is less than that of men by 14 per cent (0.34 millivolt) in the frontal, 24 per cent (0.71 millivolt) in the sagittal and 17 per cent (0.36 millivolt) in the horizontal plane.

Figs 3 and 4 show reconstructed mean QRS T deflections and vector loops comprising normal men and women. The smaller scalar deflections and vector loops in women are readily seen in these illustrations. It is also seen that mean vectors at the end of QRS (point J) are more posterior and superior in women.

Despite small mean differences the general direction of the maximal and half area QRS vectors is strikingly similar in both sexes. Mean

**Table III** Time intervals obtained from three simultaneously recorded leads. Onset and end of each electrocardiographic waveform were taken at the earliest and latest departure from the baseline in any one of the three leads

| Item                       | Measurement (sec) |
|----------------------------|-------------------|
| P duration                 | 0.10 ± 0.019      |
|                            | 0.04 → 0.14       |
| P R interval               | 0.14 ± 0.01       |
|                            | 0.12 → 0.20       |
| P R segment                | 0.018 ± 0.018     |
|                            | 0.00 → 0.09       |
| QRS duration               | 0.064 ± 0.004     |
|                            | 0.04 → 0.10       |
| Q T interval (uncorrected) | 0.72 ± 0.07       |
|                            | 0.319 → 0.47      |

ST vectors are more superiorly and posteriorly directed in women than in men (Fig 3). In contrast to men who normally have negative T waves in Lead z, women may have a flat or slightly positive T in this lead as a normal variant. The normal ranges of the maximal T vector angle in the horizontal and sagittal planes are larger in this group and extend from anterior to posterior and from inferior to superior (Table VII).

In women Q waves in Leads x and y and S waves in Lead x occur less frequently and the upper normal limit of QRS duration is 8 milliseconds shorter than in men. Mean Q wave duration in Leads x and y is also significantly shorter in this group but large variances in this parameter invalidate its use as a differential diagnostic tool.

## Discussion

Differences in electrocardiograms of men and women are frequently ignored in routine interpretations. This is mainly due to the lack of well defined sex specific normal limits.

While such limits for normal men have been well established in both conventional and orthogonal leads, a comprehensive study of the latter lead system in women is non-existent. In the largest series of normal men and women published by von der Groeben and associates, only means and standard deviations are reported which do not lend themselves to an estimate of realistic normal ranges. This is due to the fact that most of the electrocardiographic data are not

Table IV Planar amplitudes and directions of the maximal vectors and half area and instantaneous QRS vectors. Planar amplitudes of instantaneous QRS vectors are determined from scalar components (see text)

| Item                 | Frontal   |  | Left Sagittal  |   | Horizontal   |   |
|----------------------|---|--|--|---|--|---|
|                      | Amplitudes  | Angles   | Amplitudes   | Angles  | Amplitudes   | Angles                                    |
| Maximal P Vector     | 0.01 $\pm$ 0.04<br>0.04 $\rightarrow$ 0.19          | 61 $\frac{1}{2}$<br>0 $\rightarrow$ 93 $\frac{1}{2}$ | 0.10 $\pm$ 0.04<br>0.03 $\rightarrow$ 0.18           | 96<br>1 $\rightarrow$ 44                          | 0.06 $\pm$ 0.02<br>0.03 $\rightarrow$ 0.12           | 14<br>115 $\rightarrow$ -98               |
| Maximal QRS Vector   | 1.24 $\pm$ 0.38<br>0.63 $\rightarrow$ 2.19          | 41<br>10 $\rightarrow$ 88                            | 1.00 $\pm$ 0.21<br>0.49 $\rightarrow$ 1.70           | 125<br>-156 $\rightarrow$ 48                      | 1.10 $\pm$ 0.32<br>0.55 $\rightarrow$ 1.84           | 29<br>114 $\rightarrow$ -35               |
| Maximal T Vector     | 0.28 $\pm$ 0.11<br>0.10 $\rightarrow$ 0.57          | 32<br>2 $\rightarrow$ 68                             | 0.20 $\pm$ 0.08<br>0.07 $\rightarrow$ 0.42           | 62<br>170 $\rightarrow$ -88                       | 0.25 $\pm$ 0.10<br>0.09 $\rightarrow$ 0.49           | -17<br>4 $^{\circ}$ $\rightarrow$ -70     |
| Half Area QRS Vector | 1.12 $\pm$ 0.45<br>0.22 $\rightarrow$ 2.20          | 4 $^{\circ}$<br>-1 $\rightarrow$ 8 $^{\circ}$        | 0.93 $\pm$ 0.26<br>0.24 $\rightarrow$ 1.71           | 120<br>-174 $\rightarrow$ 5 $^{\circ}$            | 0.97 $\pm$ 0.33<br>0.36 $\rightarrow$ 1.70           | 29<br>78 $\rightarrow$ -22                |
| Initial QRS Vectors  |   |  |  |   |  |   |
| 0.01 second          | 0.07 $\pm$ 0.04<br>0.01 $\rightarrow$ 0.18          | -13 $\frac{1}{2}$<br>20 $\rightarrow$ -10            | 0.13 $\pm$ 0.05<br>0.03 $\rightarrow$ 0.24           | -4<br>80 $\rightarrow$ -58                        | 0.13 $\pm$ 0.05<br>0.03 $\rightarrow$ 0.24           | -95<br>-5 $\rightarrow$ -146              |
| 0.02 second          | 0.23 $\pm$ 0.17<br>0.02 $\rightarrow$ 0.69          | 28<br>-129 $\rightarrow$ 1 $\frac{1}{2}$             | 0.9 $\pm$ 0.14<br>0.04 $\rightarrow$ 0.62            | 94<br>144 $\rightarrow$ -30                       | 0.32 $\pm$ 0.14<br>0.06 $\rightarrow$ 0.69           | -54<br>38 $\rightarrow$ -115              |
| 0.03 second          | 0.78 $\pm$ 0.3 $^{\circ}$<br>0.1 $\rightarrow$ 1.51 | 34<br>1 $\rightarrow$ 64                             | 0.53 $\pm$ 0.27<br>0.04 $\rightarrow$ 1.16           | 88<br>156 $\rightarrow$ 10                        | 0.63 $\pm$ 0.27<br>0.1 $^{\circ}$ $\rightarrow$ 1.32 | -9<br>54 $\rightarrow$ -57                |
| 0.04 second          | 1.06 $\pm$ 0.45<br>0.10 $\rightarrow$ 2.00          | 39<br>-4 $\rightarrow$ 84                            | 0.84 $\pm$ 0.35<br>0.10 $\rightarrow$ 1.59           | 124<br>-168 $\rightarrow$ 4 $^{\circ}$            | 0.96 $\pm$ 0.36<br>0.10 $\rightarrow$ 1.75           | 30<br>88 $\rightarrow$ -26                |
| Terminal QRS Vectors |   |  |  |   |  |   |
| 0.01 second          | 0.08 $\pm$ 0.05<br>0.01 $\rightarrow$ 0.70          | -150 $\frac{1}{2}$<br>16 $\rightarrow$ -18           | 0.12 $\pm$ 0.06<br>0.01 $\rightarrow$ 0.24           | -112<br>-3 $^{\circ}$ $\rightarrow$ 82            | 0.11 $\pm$ 0.06<br>0.01 $\rightarrow$ 0.23           | 96 $\frac{1}{2}$<br>-98 $\rightarrow$ -36 |
| 0.02 second          | 0.18 $\pm$ 0.14<br>0.03 $\rightarrow$ 0.55          | -169 $\frac{1}{2}$<br>10 $\rightarrow$ -30           | 0.36 $\pm$ 0.16<br>0.05 $\rightarrow$ 0.69           | -17 $^{\circ}$<br>-8 $^{\circ}$ $\rightarrow$ 106 | 0.25 $\pm$ 0.17<br>0.03 $\rightarrow$ 0.7 $^{\circ}$ | 99<br>-150 $\rightarrow$ 16               |
| 0.03 second          | 0.45 $\pm$ 0.35<br>0.04 $\rightarrow$ 1.44          | 63 $\frac{1}{2}$<br>-70 $\rightarrow$ -80            | 0.64 $\pm$ 0.27<br>0.1 $^{\circ}$ $\rightarrow$ 1.24 | 163<br>-1 $^{\circ}$ $\rightarrow$ 84             | 0.66 $\pm$ 0.29<br>0.13 $\rightarrow$ 1.34           | "R"<br>150 $\rightarrow$ -5               |
| 0.04 second          | 0.90 $\pm$ 0.49<br>0.06 $\rightarrow$ 2.00          | 43<br>-5 $\rightarrow$ -160                          | 0.81 $\pm$ 0.34<br>0.19 $\rightarrow$ 1.56           | 13 $^{\circ}$<br>-140 $\rightarrow$ 54            | 0.89 $\pm$ 0.36<br>0.18 $\rightarrow$ 1.75           | 41<br>1 $^{\circ}$ $\rightarrow$ -96      |

Amplitudes are in millivolts.

Angles are in degrees. All angular ranges should be read in clockwise sequence.

Values marked by  $\frac{1}{2}$  show no significant change and need by wide 95 percent confidence ranges.

normally distributed. Ranges should preferably be expressed in terms of percentiles. In another report on sex differences in the vectorcardiogram the sample size is not large enough for determination of valid sex specific normal limits. As pointed out previously adequate sample size as well as detailed statistical analysis represents prerequisites for arriving at reliable normal standards. The present study based on the records from 510 men and 450 women should be sufficient for precise demarcation of normal limits in both sexes. Table VII summarized the most important sex differences in the electro-vector cardiographic parameters and can be used as a guideline for differentiation of normal from abnormal. Apart from spatial magnitudes all other variables presented in this table can be manually measured from any record and a comparison can be easily made with the tabulated norms.

Table V Spatial magnitude and orientation of maximal P, QRS and T vectors

| Item               | Magnitude (millivolts)                     | Azimuth (degrees)                     | Elevation (degrees)                  |
|--------------------|--|---------------------------------------|--------------------------------------|
| Maximal P Vector   | 0.11 $\pm$ 0.04<br>0.05 $\rightarrow$ 0.20 | 14<br>115 $\rightarrow$ -98           | 49<br>-2 $^{\circ}$ $\rightarrow$ 80 |
| Maximal QRS Vector | 1.35 $\pm$ 0.36<br>0.5 $\rightarrow$ 2.25  | 29<br>114 $\rightarrow$ -35           | 34<br>-5 $\rightarrow$ 61            |
| Maximal T Vector   | 0.33 $\pm$ 0.13<br>0.12 $\rightarrow$ 0.64 | -17<br>4 $^{\circ}$ $\rightarrow$ -70 | 31<br>-15 $\rightarrow$ 64           |

Angular ranges should be read in a clockwise sequence.

The larger amplitudes seen in men in practically all scalar and vectorial items indicate that diagnostic criteria of ventricular hypertrophies are of different sensitivity and specificity in men and women. For example the upper limit of normal of the sum of R and R amplitudes was found to be 2.5 millivolts and 3.1 millivolts for



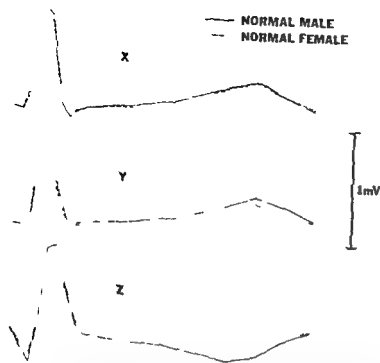


Fig 3 QRS T complexes in normal men and women. Figures are constructed from mean amplitude values of each eighth of the QRS and ST T complexes (obtained by dividing the total duration of these complexes into eight equal parts). Data are based on records from 510 normal men and 450 normal women.

Table VI Direction of inscription of QRS loops in the frontal left sagittal and horizontal planes in 450 normal women

|        | Frontal   | Left sagittal | Horizontal |
|--------|-----------|---------------|------------|
| CW     | 230 (51%) | 8 (2%)        | 0 (0%)     |
| CW/CCW | 3% (6%)   | 12 (3%)       | 0 (0%)     |
| CCW/CW | 61 (14%)  | 27 (6%)       | 8 (2%)     |
| CCW    | 122 (27%) | 403 (89%)     | 442 (98%)  |

Abbreviation: CW = clockwise; CW/CCW = figure-of-eight clockwise then counterclockwise; CCW/CW = figure-of-eight counterclockwise then clockwise; CCW = counterclockwise.

women and men respectively a difference of 24 per cent. This criterion which was found very useful in the diagnosis of left ventricular hypertrophy obviously needs to be applied differently according to the sex of the patient under study. Use of this high voltage criterion with an upper limit derived from males in a female population would decrease its sensitivity drastically.

Similar discrepancies in almost all other diagnostic parameters of left ventricular hypertrophy exist between both sexes. Low voltage criteria for diagnosis of right ventricular hypertrophy and chronic obstructive pulmonary disease are also affected significantly by these voltage differences.

Table VII Sex specific limits. Data are derived from records of 510 normal men and 450 normal women unless indicated otherwise in parentheses ( $P < .001$  for all measurements).

| Items                       | Men   | Women  |
|-----------------------------|---|--|
| <b>Scalar measurements</b>  |   |  |
| QRS duration                | $0.093 \pm 0.009$                                   | $0.084 \pm 0.008$                                  |
| Q amplitude†                | $-0.41 \pm 0.21$<br>$-0.93 \rightarrow -0.09$       | $-0.31 \pm 0.1^*$ (44)<br>$-0.7 \rightarrow -0.0$  |
| R amplitude                 | $1.17 \pm 0.37$<br>$0.51 \rightarrow 1.97$          | $0.91 \pm 0.3$<br>$0.15 \rightarrow 1.7$           |
| R amplitude                 | $1.03 \pm 0.41$<br>$0.3 \rightarrow 1.9$            | $0.81 \pm 0.33$<br>$0.2 \rightarrow 1.5$           |
| R amplitude                 | $0.93 \pm 0.3$<br>$0.36 \rightarrow 1.79$           | $0.68 \pm 0.2$<br>$0.22 \rightarrow 1.2$           |
| S amplitude                 | $-0.27 \pm 0.15$ (407)<br>$-0.68 \rightarrow -0.06$ | $-0.17 \pm 0.11$ (119)<br>$-0.4 \rightarrow -0.01$ |
| T amplitude                 | $-0.29 \pm 0.13$<br>$-0.8 \rightarrow -0.18$        | $-0.08 \pm 0.10$<br>$-0.31 \rightarrow 0.10$       |
| Q/R amplitude ratio         | $0.30 \pm 0.2$<br>$0.10 \rightarrow 1.20$           | $0.51 \pm 0.4^*$ (44)<br>$0.10 \rightarrow 1.7$    |
| R + R amplitude             | $2.00 \pm 0.52$<br>$1.0 \rightarrow 3.10$           | $1.60 \pm 0.4^*$<br>$0.8 \rightarrow 2.5$          |
| point J in Lead z           | $-0.07 \pm 0.04$<br>$-0.17 \rightarrow 0.00$        | $-0.01 \pm 0.03$<br>$-0.07 \rightarrow 0.04$       |
| <b>Planar measurements</b>  |   |  |
| Max QRS amplitude           | $1.57 \pm 0.42$<br>$0.81 \rightarrow 2.3$           | $1.24 \pm 0.34$<br>$0.63 \rightarrow 2.19$         |
| Max QRS amplitude           | $1.32 \pm 0.4$<br>$0.60 \rightarrow 2.42$           | $1.00 \pm 0.31$<br>$0.49 \rightarrow 1.7$          |
| Max QRS amplitude           | $1.39 \pm 0.4$<br>$0.74 \rightarrow 2.19$           | $1.10 \pm 0.31$<br>$0.5 \rightarrow 1.83$          |
| Max T amplitude             | $0.36 \pm 0.13$<br>$0.13 \rightarrow 0.6$           | $0.31 \pm 0.08$<br>$0.07 \rightarrow 0.4$          |
| Max T amplitude             | $0.40 \pm 0.14$<br>$0.15 \rightarrow 0.72$          | $0.2$<br>$0.07 \rightarrow 0.49$                   |
| Max T angle‡                | 38<br>$8^{\circ} \rightarrow 0$                     | 6<br>$1^{\circ} \rightarrow -84$                   |
| Max T angle                 | -46<br>$-8 \rightarrow -83$                         | -1<br>$4^{\circ} \rightarrow 0$                    |
| <b>Spatial measurements</b> |   |  |
| Max QRS magnitude           | $1.71 \pm 0.41$<br>$0.97 \rightarrow 2.7$           | $1.3 \pm 0.3$<br>$0.7 \rightarrow 2.2$             |
| Max T magnitude             | $0.46 \pm 0.16$<br>$0.18 \rightarrow 0.7$           | $0.31 \pm 0.12$<br>$0.07 \rightarrow 0.7$          |

Duration are in seconds.

†Amplitudes are in millivolts.

‡Angles are in degrees.

The lower limit of normal for R had been found the most useful criterion both for right ventricular hypertrophy and chronic obstructive pulmonary disease. In men this limit was 0.51 millivolt and in women 0.35 millivolt. If the limit of normal for men was to be applied to a normal female population it is obvious that a substantial number of the latter would be erroneously diag-

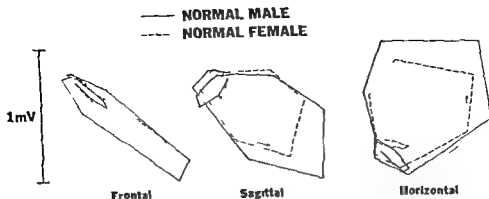


Fig 4 QRS-T loops in three plane projections. Figures are constructed from mean planar amplitudes of 4 divisions of QRS and ST-T complexes. Data are derived from 510 normal men and 450 normal women.

sified as abnormal with a tentative diagnosis of right ventricular hypertrophy or chronic obstructive pulmonary disease. These examples indicate that to improve diagnostic performance of the electrocardiogram sex specific limits for high and low voltage are necessary.

The smaller amplitudes in women have been ascribed to differences in torso size, higher content of body fat, and smaller average heart size. The mean left ventricular mass was found to be significantly smaller in women than in men.<sup>2</sup> The average heart weight was 312 Gm in normal males and 226 Gm in normal females. The smaller heart size may also explain the significantly shorter QRS duration seen in women. This difference in duration signifies the importance of sex specific limits in the diagnosis of ventricular conduction delays.

Scalar analysis shows that in approximately one half of the normal women and one third of the normal men no Q wave in the x and y leads can be found. A similar observation in conventional electrocardiograms has been reported by Simonson.<sup>3</sup> The absence of the Q wave in these leads is so common in all age and sex groups that no diagnostic significance should be given to this observation. Comparative analysis of the Q wave in Lead z shows that initial anterior QRS forces are of lower magnitude in normal women and in 1 per cent of the cases may even be absent in this lead. This confirms the finding in the conventional electrocardiogram of a higher incidence of absent initial R waves in some of the right precordial lead in women. Such a finding is extremely rare in men. The normal electrocardiogram of women therefore should not be confused with antero-septal myocardial infarction.

which reveal similar electrocardiographic features. The occurrence of an S wave in Lead z in the presence of normal QRS duration should be considered a normal variant. This pattern is more commonly seen in younger adults. A delay in activation of the right ventricle has been postulated as its cause.

The more superiorly and posteriorly directed point J and ST segment in women may play a role in diagnostic interpretations of exercise electrocardiograms and ischemic patterns. Differences found between men and women in the electrocardiographic response to exercise<sup>2</sup> are probably due to these inherent sex differences in the ST segment of the resting electrocardiogram. Although the resting electrocardiogram usually serves as control for the exercise response in each individual case, the specificity and sensitivity of the test may be enhanced if the criteria of interpretation were modified.

Our observation in women of a less anteriorly directed mean maximal T vector in the horizontal plane is comparable to findings by Simonson<sup>3</sup> of a negative mean T wave amplitude in Lead V<sub>1</sub>.

Some abnormal rotation of the QRS loops was observed in a few of the elderly subjects. In this group a certain degree of myocardial fibrosis, clinically silent scars, and/or fascicular blocks cannot be entirely ruled out. It is pertinent to note that a relatively high incidence of left anterior hemiblock in the elderly without manifest cardiovascular diseases has been reported in the literature.<sup>4</sup> For the diagnosis of fascicular blocks it is important to realize that normal ranges of maximal QRS vectors differ considerably from ranges derived from conventional 12 lead electrocardiograms. Whereas for standard leads a range

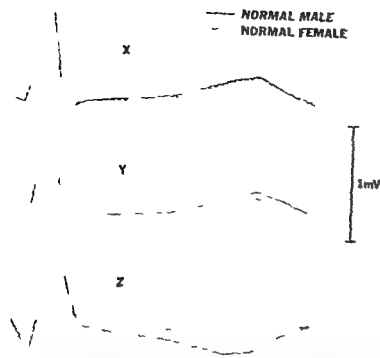


Fig 3 QRS-T complexes in normal men and women. Figures are constructed from mean amplitude values of each eighth of the QRS and ST-T complexes (obtained by dividing the total duration of these complexes into eight equal parts). Data are based on records from 510 normal men and 450 normal women.

Table VI Direction of inscription of QRS loops in the frontal, left sagittal and horizontal planes in 450 normal women

|        | Frontal   | Left sagittal | Horizontal |
|--------|-----------|---------------|------------|
| CW     | 230 (51%) | 8 (2%)        | 0 (0%)     |
| CW CCW | 17 (4%)   | 12 (3%)       | 0 (0%)     |
| CCW CW | 61 (14%)  | 27 (6%)       | 8 (2%)     |
| CCW    | 122 (27%) | 403 (89%)     | 442 (99%)  |

Abbreviation: CW = clockwise; CCW = figure-of-eight clockwise; then counterclockwise; CCW = figure-of-eight counterclockwise; then clockwise; CCW = counterclockwise.

women and men respectively a difference of 24 per cent. This criterion which was found very useful in the diagnosis of left ventricular hypertrophy obviously needs to be applied differently according to the sex of the patient under study. Use of this high voltage criterion with an upper limit derived from males in a female population would decrease its sensitivity drastically.

Similar discrepancies in almost all other diagnostic parameters of left ventricular hypertrophy exist between both sexes. Low voltage criteria for diagnosis of right ventricular hypertrophy and chronic obstructive pulmonary disease are also affected significantly by these voltage differences.

Table VII Sex specific limits. Data are derived from records of 510 normal men and 450 normal women unless indicated otherwise in parentheses ( $P < 0.01$  for all measurements).

| Items                       | Men                    | Women                  |
|-----------------------------|------------------------|------------------------|
| <b>Scalar measurements</b>  |                        |                        |
| QRS duration                | $0.093 \pm 0.009$      | $0.091 \pm 0.009$      |
| Q amplitude†                | $-0.41 \pm 0.21$       | $-0.31 \pm 0.11$ (44)  |
| R amplitude                 | $1.17 \pm 0.37$        | $0.91 \pm 0.33$        |
| R amplitude                 | $1.03 \pm 0.41$        | $0.81 \pm 0.33$        |
| R amplitude                 | $0.93 \pm 0.33$        | $0.79 \pm 0.33$        |
| S amplitude                 | $-0.27 \pm 0.15$ (40%) | $-0.17 \pm 0.11$ (11%) |
| T amplitude                 | $-0.24 \pm 0.13$       | $-0.04 \pm 0.10$       |
| Q/R amplitude ratio         | $0.50 \pm 0.31$        | $0.51 \pm 0.47$ (46)   |
| R + R amplitude             | $2.00 \pm 0.12$        | $1.60 \pm 0.47$        |
| point J in Lead z           | $-0.07 \pm 0.04$       | $-0.01 \pm 0.03$       |
|                             | $-0.17 \pm 0.00$       | $-0.07 \pm 0.04$       |
| <b>Planar measurements</b>  |                        |                        |
| Max QRS amplitude           | $1.57 \pm 0.42$        | $1.21 \pm 0.34$        |
| Max QRS amplitude           | $0.81 \pm 0.23$        | $0.73 \pm 0.19$        |
| Max QRS amplitude           | $1.32 \pm 0.43$        | $1.00 \pm 0.31$        |
| Max QRS amplitude           | $0.63 \pm 0.24$        | $0.49 \pm 0.17$        |
| Max QRS amplitude           | $1.39 \pm 0.36$        | $1.10 \pm 0.31$        |
| Max T amplitude             | $0.74 \pm 0.19$        | $0.51 \pm 0.13$        |
| Max T amplitude             | $0.36 \pm 0.13$        | $0.20 \pm 0.08$        |
| Max T amplitude             | $0.13 \pm 0.07$        | $0.07 \pm 0.04$        |
| Max T amplitude             | $0.40 \pm 0.14$        | $0.25 \pm 0.10$        |
| Max T amplitude             | $0.15 \pm 0.07$        | $0.09 \pm 0.07$        |
| Max T angle‡                | 38°                    | 0°                     |
| Max T angle                 | 8°                     | 17°                    |
| Max T angle                 | -4°                    | -1°                    |
| Max T angle                 | -2°                    | -3°                    |
| Max T angle                 | 4°                     | -7°                    |
| <b>Spatial measurements</b> |                        |                        |
| Max QRS magnitude           | $1.73 \pm 0.44$        | $1.07 \pm 0.34$        |
| Max T magnitude             | $0.92 \pm 0.27$        | $0.73 \pm 0.19$        |
| Max T magnitude             | $0.46 \pm 0.16$        | $0.30 \pm 0.11$        |
| Max T magnitude             | $0.18 \pm 0.06$        | $0.09 \pm 0.03$        |

Durations are in seconds.  
†Amplitudes are in mV.  
‡Angles are in degrees.

The lower limit of normal for R had been found the most useful criterion both for right ventricular hypertrophy and chronic obstructive pulmonary disease. In men this limit was 0.1 mV, and in women 0.3 mV. If the limit of normal for men was to be applied to a normal female population it is obvious that a substantial number of the latter would be erroneously

10. Riekkonen H., and Rautaharju I. M. Body position, electrode level, and respiration effects on the Frank lead electrocardiogram. *Circulation* 53:40, 1976.
11. Pipberger H. V. Computer analysis of the electrocardiogram. in *Computers in biomedical research* vol 1 edited by R. W. Stacy and H. D. Waxman. New York 1967. Academic Press p. 377.
12. Pipberger H. V., McCaughan D., Littmann D., Pipberger H. A., Cornfield J., Dunn R. A., Batchlor C. D., and Berson A. S. Clinical application of a second generation electrocardiographic computer program. *Am J Cardiol* 35:597, 1975.
13. Pipberger H. V. et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Report of the Committee on Electrocardiography. American Heart Association. *Circulation* August 1970. News from the American Heart Association pp. 11-31.
14. Pipberger H. V. Evaluation of quantitative methods for obtaining mean spatial QRS vectors. *Circulation* 16:976, 1957.
15. Foblete P. F., Hunt P. M., Batchlor C. D., and Pipberger H. V. Evaluation of frontal plane QRS loop rotation in vectorcardiographic diagnosis. *J Electrocardiol* 7:28, 1974.
16. Ratschelet E. Statistical methods for the analysis of problems in animal orientation and certain biological rhythms. Washington D. C. 1965. American Institute of Biological Sciences.
17. Watson G. S., and Williams E. J. On the construction of significance tests on the circle and the sphere. *Biometrika* 43:344, 1956.
18. McCaughan, D., Littmann D., and Pipberger H. V. Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in 979 cases with hypertensive cardiovascular disease. *Am Heart J* 88:467, 1973.
19. Pipberger H. V., Schneiderman M. A., and Klingeman J. D. The love at first sight effect in research. *Circulation* 38:877, 1968.
20. Simonson E. Principles and pitfalls in establishing normal electrocardiographic limits. *Am J Cardiol* 33:71, 1974.
21. Kerr A. Jr., Adcock A., Klingeman J. D., and Pipberger H. V. Computer analysis of the orthogonal electrocardiogram in pulmonary emphysema. *Am J Cardiol* 25:34, 1970.
22. Kennedy J. W., Baxley W. A., Figley M. M., Dodge H. T., and Blackburn J. R. Quantitative angio cardiography I. The normal left ventricle in man. *Circulation* 34:712, 1966.
23. Gould S. E. Pathology of the heart and blood vessels. Springfield, Ill. 1968. Charles C. Thomas Publisher p. 93.
24. Lepeschkin E. Physiological factors influencing the electrocardiographic response to exercise in measurement in exercise electrocardiography. The Ernst Simonson Conference, edited by H. Blackburn. Springfield, Ill. 1969. Charles C. Thomas Publisher p. 363.
25. Astrand, I. Exercise electrocardiograms recorded twice with an 8-year interval in a group of 704 women and men, 48-63 years old. *Acta Med Scand* 178:77, 1965.
26. Bruce R. A. Values and limitations of exercise electrocardiography. *Circulation* 50:118, 1974.
27. Blomquist C. G. Use of exercise testing for diagnostic and functional evaluation of patients with arteriosclerotic heart disease. *Circulation* 44:1170, 1971.
28. Sketch, M. H., Mohiuddin S. M., Lynch J. D., Zenzka A. E., and Fungo V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol* 38:189, 1970.
29. Simonson E., Blackburn H. Jr., Puchner T. C., Eisenberg I., Ribeiro F., and Meja M. Sex differences in the electrocardiogram. *Circulation* 22:598, 1960.
30. Mahalik M. J., and Fitch C. Electrocardiographic findings in the aged. *Am Heart J* 87:11, 1974.

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material."

from  $-30$  to  $+110$  degrees is considered normal for QRS direction in the frontal plane, the normal range for orthogonal leads extends only from  $10$  to  $75$  degrees in males and from  $10$  to  $88$  degrees in females. For the diagnosis of left anterior and posterior hemiblock, appropriate normal limits need to be used to detect abnormal left and right axis deviations.

The normal limits of the orthogonal electrocardiogram in women presented here clearly demonstrate the importance of sex specific electrocardiographic criteria for diagnosis of ventricular hypertrophies and conduction delays. The fact that the Q wave in Lead  $z$  may be absent in some of the normal women should be considered in evaluation of electrocardiograms for antero-septal myocardial infarctions. Furthermore, in the detection of coronary artery disease the electrocardiographic response to exercise may achieve a higher degree of sensitivity and specificity if interpreted in the context of the appropriate limits of normal for men and women.

### Summary

Normal limits of the orthogonal electrocardiogram and vectorcardiogram in adult women, ranging in age from  $18$  to  $90$  years, are presented. A comparison of results is made with those of normal age matched men and sex differences are analyzed from a total of  $960$  normal records ( $510$  men and  $450$  women). For the majority of scalar and vectorial items, significant sex differences were found which in women included shorter QRS duration, smaller vector loops and decreased P, Q, R, S and T deflections. The upper normal limits of R, R<sub>1</sub>, and R<sub>2</sub> amplitudes were  $11$  per cent,  $20$  per cent and  $30$  per cent less respectively in women than in men.

The sensitivity and specificity of electrocardiographic criteria for high and low voltage were significantly affected by these sex differences in amplitudes. For example as a discriminator between normals and subjects with left ventricular hypertrophy, the upper normal limit of R + R<sub>1</sub> amplitude sum was  $3.10$  millivolts in men but  $2.50$  millivolts in women. Hence the use of the limit derived from males in a female population would decrease its sensitivity drastically. Similar discrepancies existed in the sensitivity and specificity of electrocardiographic criteria for low voltage. Since the lower normal limit of R<sub>2</sub> amplitude was  $0.51$  millivolt in men

but only  $0.35$  millivolt in women, a substantial number of normal women would be misclassified as having right ventricular hypertrophy or chronic obstructive pulmonary disease if the limit derived from males was used as a criterion.

The absence of Q waves in Leads  $x$  and  $y$  was a common finding in each age and sex group and carries no diagnostic significance. While initial anterior QRS forces in Lead  $z$  were present in all normal men, they were smaller and even absent in  $1$  per cent of normal women. Hence greater difficulties in electrocardiographic diagnosis of antero-septal myocardial infarction in women may be encountered.

Mean vectors at the end of QRS (point J) and early part of the ST segment were more inferior and anteriorly directed in men than in women. T waves in Lead  $z$  were always negative in men but flat or positive T waves were observed in some of the normal women. Sex differences in the level of point J and the ST segment may have important bearings on the interpretation of exercise electrocardiograms.

The shorter QRS duration in women signified the importance of sex specific limits for ventricular conduction delays.

The authors gratefully acknowledge the valuable assistance of Mrs. Ruby Harris, Mrs. Grace Oliver and Ms. Catherine Bader for the computations.

### REFERENCES

1. van der Grienden J, Fisher D D, and Tonle J C. Temporo-spatial frequency distribution of I, Q, R, S and T in normal man and woman. *AM HEART J* 75: 65, 1968.
2. Sotobata I, Richman H, and Simonson F. Sex differences in the vectorcardiogram. *Circulation* 37: 43, 1968.
3. Witham A C, and Lehman J J. Vectorcardiogram post forty. *AM HEART J* 79: 147, 1970.
4. Simonson F. Differentiation between normal and abnormal in electrocardiography. St. Louis, 1961. The C.V. Mosby Company.
5. Frank E. An accurate clinically practical system for spatial vectorcardiography. *Circulation* 32: 37, 1965.
6. Strayer H W, Feffer C J, Stallmann F W, Littmann D., and Pipberger H V. The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system). *Circulation* 30: 3, 1964.
7. Grubb E A, McFarland R A., Gates D C, and Webster F A. Analysis of the electrocardiogram obtained from 1000 young healthy aviators. *AM HEART J* 27: 4, 1944.
8. How E L, Lamb L E, and Allen M E. Electrocardiographic findings in ECG's of a representative group of normal values. *Am J Cardiol* 16: 70, 1961.
9. Altman E L, and D. Coste D. A comparison of the ECG Lead I and III method with the method of the ECG. *Annals of American Association for Experimental Biology* p. 164.

Table 1 Clinical and electrophysiologic data

| Pt no            | Age | Diagnosis | Resting ECG           | Sinus CL (msec) | A H (msec) | H V (msec) | Antegrade conduction | Retrograde conduction     |
|------------------|-----|-----------|-----------------------|-----------------|------------|------------|----------------------|---------------------------|
| <b>Group I</b>   |     |           |                       |                 |            |            |                      |                           |
| 1                | 55  | PSVT      | Normal                | 1250            | 100        | 55         | WP at ACL 665 msec   | 1:1 VA up to VCL 375 msec |
| 2                | 30  | PSVT      | Normal                | 680             | 65         | 50         | 315                  | 335                       |
| 3                | 60  | PSVT      | RBBB                  | 880             | 85         | 50         | 400                  | 375                       |
| 4                | 34  | PSVT      | Normal                | 800             | 75         | 45         | 315                  | 360                       |
| 5                | 50  | PSVT      | RBBB                  | 700             | 100        | 50         | 325                  | 375                       |
| 6                | 47  | PSVT      | Normal                | 900             | 115        | 50         | 430                  | 350                       |
| 7                | 65  | ASHD      | AMI                   | 1170            | 115        | 50         | 430                  | WP at VCL 400             |
| 8                | 61  | ASHD      | Normal                | 900             | 100        | 50         | 300                  | 1:1 VA up to VCL 350      |
| 9                | 57  | PSVT      | Normal                | 80              | 10         | 50         | 400                  | 370                       |
| 10               | 0   | ASHD      | Normal                | 1000            | 125        | 40         | 600                  | 370                       |
| 11               | 46  | PSVT      | Normal                | 900             | 90         | 40         | 400                  | WP at VCL 460             |
| 12               | 68  | ASHD      | LBBB                  | 700             | 10         | 65         | 545                  | 30                        |
| 13               | 57  | PSVT      | Normal                | 800             | 80         | 50         | 380                  | 300                       |
| <b>Group II</b>  |     |           |                       |                 |            |            |                      |                           |
| 14               | 50  | PSVT      | Normal                | 700             | 110        | 50         | 475                  | 1:1 VA at VCL 300         |
| 15               | 54  | ASHD      | IMI                   | 80              | 80         | 40         | 460                  | 300                       |
| 16               | 17  | PSVT      | Normal                | 600             | 100        | 40         | 400                  | 335                       |
| 17               | 14  | PSVT      | Normal                | 680             | 80         | 45         | 400                  | 350                       |
| <b>Group III</b> |     |           |                       |                 |            |            |                      |                           |
| 18               | 47  | PSVT      | Normal                | 840             | 85         | 40         | WP at ACL 400        | WP at VCL 600             |
| 19               | 55  | PSVT      | Normal                | 700             | 75         | 40         | 330                  | 1:1 VA up to VCL 315      |
| 20               | 49  | ASHD      | ST & T Abnor malities | 670             | 0          | 60         | 315                  | 370                       |

ASHD = arterial disease; IMI = inferior myocardial infarction; AMI = anterior myocardial infarction; RBBB = right bundle branch block; LBBB = left bundle branch block; ACL = atrioventricular conduction; WP = Wenckebach phenomenon; 1:1 VA = atrioventricular conduction; 1:1 AV = atrioventricular conduction; Pt no = patient number

graphic paper at a speed of 150 mm/sec. Using a programmed digital stimulator, incremental atrial and ventricular pacing was performed up to the onset of Ant and Ret Wenckebach phenomenon or up to maximum heart rates of 200 beats/min. For refractory period determinations, comparable basic atrial and ventricular cycle lengths (A-A or V-V) were scanned with programmed extra stimuli (A or V) at decreasing coupling intervals (A-A or V-V) up to the point of atrial or ventricular muscle refractoriness. Care was taken to ground all equipment. All procedures were completed without any complications.

#### Definition of terms

The definitions for Ant and Ret conduction times and refractory periods have been published. For the present study, the following

additional measurements were made. The interval between the Ant His (H) bundle potential and the subsequent atrial echo response (H-Ae interval) during PSVT was measured both from the onset and the end of H to the onset of low right atrial deflection on the His bundle electrogram (HBE) recording. Similarly, the following Ae-H interval was measured from the onset of respective deflections. The onset of the low right atrial electrogram during the Ae or PSVT was relatively easy to identify when the Ae coincided preceded or clearly followed the ventricular electrogram as occurred in 16 out of 20 patients. In the remaining four patients, the onset of Ae on the HBE was obscured by the ventricular electrogram and the H-Ae interval had to be measured indirectly. In these cases, the H-Ae interval was measured from the H to the onset of the high

# Antegrade and retrograde conduction characteristics in three patterns of paroxysmal atrioventricular junctional reentrant tachycardia

Masood Akhtar, M D \*

Anthony N Damato M D

Jeremy N Ruskin M D

William P Batsford, M D

C Pratap Reddy M D

Andres R Tizon, M D

Malkiat S Dhatt, M D

Joseph A C Gomes M D

Antonino H Calon M D

Staten Island N Y

In recent years the electrophysiology of paroxysmal atrioventricular junctional reentrant supraventricular tachycardia (PSVT) has been frequently studied.<sup>1-4</sup> The term PSVT has been used in a broad sense and only recently has it been realized that the site of reentry may not necessarily be the atrioventricular (A-V) node.<sup>5-11</sup> With few exceptions most studies of PSVT have dealt with the analysis of antegrade (Ant) conduction. Only rarely have either the capacity or the patterns of ventriculo atrial (V-A) conduction been documented in these patients. The present study deals with both Ant and retrograde (Ret) conduction characteristics in 20 patients with documented PSVT in the absence of ventricular pre-excitation. The purposes of this report are as follows: (1) to describe three distinct patterns of PSVT based upon the relationship

between Ant-His (H) bundle activation and atrial echo response (Ae) during PSVT; (2) to offer a rather simple and reproducible method i.e. Ant and Ret conduction ratios (Ae:H:H:Ae) for determining the site of reentry during PSVT; and (3) to provide comparisons and correlations of Ant and Ret conduction and refractory period patterns in patients with PSVT. In addition some interesting and controversial aspects of PSVT will be discussed.

## Materials and Methods

Right heart catheterization was performed in the nonsedated postabsorptive state. The nature of the study was explained to all patients and signed consent obtained. Electrode catheters were fluoroscopically positioned in the region of the high right atrium, tricuspid valve and right ventricular apex for recording local electrical activity and electrical stimulation.<sup>12-14</sup> When feasible an additional electrode catheter was positioned in the region of the mid coronary sinus. All intracardiac electrograms (filtered at frequency settings of 40 to 500 Hz) standard ECG Leads I, II and V<sub>1</sub> and time lines generated at 10, 100 and 1000 msec were displayed on a multichannel oscilloscope and recorded on magnetic tape. The records were subsequently reproduced on photo

From the Cardiology Department, United States Public Health Service Hospital, Staten Island, N.Y.

This work was supported in part by the Bureau of Medical Services, National Heart, Lung and Blood Institute Project HL 12-30-0.

Received for publication Aug. 16, 1976.

Accepted for publication Nov. 8, 1976.

Reprint requests: Anthony N. Damato, M.D., Cardiology Department, United States Public Health Service Hospital, Staten Island, N.Y. 10314.

Present address: Cardiovascular Disease Section, 111-Mount Sinai Medical Center, Milwaukee, Wis. 53201.

Table I Clinical and electrophysiologic data

| Pt. no           | Age | Diagnosis | Resting ECG           | Sinus CL (msec) | AH (msec) | HV (msec) | Antegrade conduction | Retrograde conduction     |
|------------------|-----|-----------|-----------------------|-----------------|-----------|-----------|----------------------|---------------------------|
| <b>Group I</b>   |     |           |                       |                 |           |           |                      |                           |
| 1                | 55  | PSVT      | Normal                | 1950            | 100       | 50        | WP at ACL 660 msec   | 1:1 VA up to VCL 375 msec |
| 2                | 30  | PSVT      | Normal                | 680             | 65        | 50        | 315                  | 335                       |
| 3                | 60  | PSVT      | RBBB                  | 880             | 85        | 50        | 400                  | 375                       |
| 4                | 34  | PSVT      | Normal                | 800             | 70        | 45        | 315                  | 360                       |
| 5                | 50  | PSVT      | RBBB                  | 700             | 100       | 55        | 375                  | 375                       |
| 6                | 41  | PSVT      | Normal                | 900             | 115       | 50        | 430                  | 350                       |
| 7                |     | ASHD      | AMI                   | 1170            | 115       | 50        | 430                  | WP at VCL 400             |
| 8                | 61  | ASHD      | Normal                | 900             | 100       | 50        | 300                  | 1:1 VA up to VCL 350      |
| 9                | 57  | PSVT      | Normal                | 180             | 170       | 50        | 400                  | 370                       |
| 10               | 0   | ASHD      | Normal                | 1000            | 120       | 40        | 600                  | 370                       |
| 11               | 46  | PSVT      | Normal                | 900             | 90        | 45        | 400                  | WP at VCL 460             |
| 12               | 68  | ASHD      | LBBB                  | 700             | 100       | 65        | 545                  | 370                       |
| 13               | 57  | PSVT      | Normal                | 800             | 85        | 55        | 380                  | 300                       |
| <b>Group II</b>  |     |           |                       |                 |           |           |                      |                           |
| 14               | 50  | PSVT      | Normal                | 700             | 110       | 50        | 475                  | 1:1 VA at VCL 350         |
| 15               | 54  | ASHD      | IMI                   | 180             | 80        | 40        | 460                  | 300                       |
| 16               | 1   | PSVT      | Normal                | 600             | 100       | 45        | 400                  | 330                       |
| 17               | 14  | PSVT      | Normal                | 680             | 80        | 45        | 1:1 AV up to ACL 350 | 300                       |
| <b>Group III</b> |     |           |                       |                 |           |           |                      |                           |
| 18               | 47  | PSVT      | Normal                | 840             | 80        | 40        | WP at ACL 400        | WP at VCL 600             |
| 19               | 79  | PSVT      | Normal                | 700             | 75        | 40        | 330                  | 1:1 VA up to VCL 370      |
| 20               | 48  | ASHD      | ST & T Abnor malities | 870             | 0         | 50        | 315                  | 370                       |

ASHD = atherosclerotic heart disease; PSVT = paroxysmal reentrant supraventricular tachycardia; AMI = anterior myocardial infarct; n = number of patients; RBBB = right bundle branch block; LBBB = left bundle branch block; ACL = atrioventricular cycle length; WP = Wenckebach phenomenon; A-V = atrioventricular conduction; V-A = ventriculoatrial conduction; Pt. no. = patient number.

graphic paper at a speed of 150 mm/sec. Using a programmed digital stimulator, incremental atrial and ventricular pacing was performed up to the onset of Ant and Ret Wenckebach phenomenon or up to maximum heart rates of 200 beats/min. For refractory period determinations comparable basic atrial and ventricular cycle lengths (A-A or V-V) were scanned with programmed extrastimuli (A or V) at decreasing coupling intervals (A-A or V-V) up to the point of atrial or ventricular muscle refractoriness. Care was taken to ground all equipment. All procedures were completed without any complications.

#### Definition of terms

The definitions for Ant and Ret conduction times and refractory periods have been published. For the present study, the following

additional measurements were made. The interval between the Ant His (H) bundle potential and the subsequent atrial echo response (H-Ae interval) during PSVT was measured both from the onset and the end of H to the onset of low right atrial deflection on the His bundle electrogram (HBE) recording. Similarly, the following Ae-H interval was measured from the onset of respective deflections. The onset of the low right atrial electrogram during the Ae or PSVT was relatively easy to identify when the Ae coincided preceded or clearly followed the ventricular electrogram as occurred in 16 out of 20 patients. In the remaining four patients, the onset of Ae on the HBE was obscured by the ventricular electrogram and the H-Ae interval had to be measured indirectly. In these cases, the H-Ae interval was measured from the H to the onset of the high



Table II

| Pt<br>no  | Cyck length<br>PSVT (Ae Ae)<br>interval (msec) |     | H Ae<br>interval<br>(msec) |         | Range<br>of Ae H<br>interval<br>(msec) | H Ae Ae H     | Retrograde<br>H A interval<br>corrected for<br>rate<br>of PSVT |         | Termination<br>PSVT |  |
|-----------|--|-----|----------------------------|---------|--|---------------|--|---------|---------------------|--|
|           | Range  | At  | Onset H                    | End H   |  |               | End H  | Onset H |                     |  |
| Group I   |  |     |                            |         |  |               |  |         |                     |  |
| 1         | 460-550  | 490 | 55                         | 30      | 410-480                                | 1 7 4 8 7     | 70   | 90      | Ant block           |  |
| 2         | 260-330  | 280 | 65                         | 50      | 190-270                                | 1 3 0 3 8     | 82   | 100     | Ant block           |  |
| 3         | 430-450  | 440 | 80-80                      | 60-65   | 345-360                                | 1 4 2 4 5     | 100  | 110     | Ant block           |  |
| 4         | 325-375  | 340 | 40                         | 20      | 290-335                                | 1 1 1 8 3     | 61   | 80      | Ant block           |  |
| 5         | 335-390  | 360 | 55                         | 30      | 290-330                                | 1 5 0 6 0     | 60   | 80      | Ant block           |  |
| 6         | 580  | 580 | 30                         | 20      | 550                                    | 1 1 7 3       | 40   | 60      | Ant block           |  |
| 7         | 450  | 450 | 40                         | 20      | 400                                    | 1 9           | 55   | 70      | Ant & ret block     |  |
| 8         | 330-340  | 335 | 60                         | 60      | 200-260                                | 1 3 1 3 2     | 115  | 130     | Ant block           |  |
| 9         | 390-420  | 405 | 50                         | 30      | 340-370                                | 1 6 8 7 4     | 60   | 80      | Ant block           |  |
| 10        | 470-550  | 515 | 35                         | 15      | 445-515                                | 1 1 2 7 1 4 7 | 45   | 60      | Ant block           |  |
| 11        | 390-415  | 405 | 55                         | 30      | 340-360                                | 1 6 1 6 5     | 60   | 80      | Ret block           |  |
| 12        | 475-500  | 490 | 40                         | 25      | 435-460                                | 1 1 0 8 1 1 5 | 45   | 60      | Ant block           |  |
| 13        | 345-390  | 370 | 60                         | 30      | 290-340                                | 1 5 9 6 8     | 70   | 90      | Ant block           |  |
| Group II  |  |     |                            |         |  |               |  |         |                     |  |
| 14        | 460-480  | 470 | 200                        | 185     | 260-280                                | 1 1 3 1 4     | —  | —       | Ant block AVN       |  |
| 15        | 370-400  | 390 | 150                        | 130     | 220-250                                | 1 1 5 1 7     | —  | —       | Ant block AVN       |  |
| 16        | 280-370  | 320 | 145                        | 120     | 135-230                                | 1 1 0 1 5     | —  | —       | Ant block AVN       |  |
| 17        | 270-350  | 310 | 175                        | 155     | 90-170                                 | 1 0 5 1 0     | —  | —       | Ant block HPN       |  |
| Group III |  |     |                            |         |  |               |  |         |                     |  |
| 18        | 480-570  | 555 | 440-470                    | 420-450 | 100-140                                | 1 0 2 0 3     | 170-190  | 190-210 | Ret block           |  |
| 19        | 370-435  | 400 | 270-330                    | 205-320 | 100                                    | 1 0 3 0 4     | 60   | 80      | Ret block           |  |
| 20        | 410-470  | 430 | 300-360                    | 280-300 | 110                                    | 1 0 3 0 4     | 90   | 110     | Ret block           |  |

right atrial electrogram and the interval between the low and high right atrial electrogram as determined during Ret refractory period studies was deducted from the above value. The accuracy of such measurements was considered valid only if the sequence of Ret atrial activation during PSVT and Ret refractory period studies was the same and there was no evidence of intra atrial conduction delay, which was the case in all patients.

## Results

The essential data are summarized in Tables I to III. Patients with ventricular pre-excitation (Wolff Parkinson White Syndrome) were excluded. At the time of study all patients were in sinus rhythm and had not been taking any cardioactive medication for a period of 7 days. All patients had documented episodes of PSVT. The reentrant nature of the arrhythmia was suggested by the ability to initiate and terminate the PSVT with properly timed atrial premature beats.

For all episodes of tachycardia the interval

from the onset of H to the onset of Ae (H Ae interval) was measured and correlated with the Ae to subsequent H interval. Analysis of the H Ae and Ae H intervals and their ratios (ie H Ae Ae H) permitted classification of patients into three groups.

In group I (13 patients nos 1 to 13 Tables I to III) the H Ae and Ae H intervals averaged 52.5 and 36.1 msec respectively (range 30 to 80 msec and 19.5 to 55.0 msec respectively). The H Ae Ae H interval ratios were 1.31.73. Thus for all episodes of PSVT the H Ae values were relatively short compared to the Ae H values.

In Group II (four patients, Nos 14 to 17 Tables I to III) the H Ae intervals averaged 167.5 msec (range 145 to 200 msec) whereas the Ae H intervals had an average value of 203.7 msec (range 95 to 280 msec). The H Ae Ae H were 1.05.17. In Group II the H Ae intervals were relatively longer and the Ae H intervals relatively shorter than in Group I.

In Group III (three patients Nos 18 to 20 Tables I to III) the H Ae and Ae H interval

Table III Refractory period data

| Table III Refractory period data |                                |                             |                                     |                             |     |     |                              |       |      |                             |     |     |                              |       |      |
|----------------------------------|--------------------------------|-----------------------------|-------------------------------------|-----------------------------|-----|-----|------------------------------|-------|------|-----------------------------|-----|-----|------------------------------|-------|------|
| Pt no                            | Cycle length A-A or V-V (msec) | Echo or PSVT one A-A (msec) | Critical range A-H intervals (msec) | Antegrade                   |     |     |                              |       |      | Retrograde                  |     |     |                              |       |      |
|                                  |                                |                             |                                     | Effective refractory period |     |     | Functional refractory period |       |      | Effective refractory period |     |     | Functional refractory period |       |      |
|                                  |                                |                             |                                     | A                           | AVN | HPS | AVN                          | HPS   | AVCS | V                           | AVN | HPS | AVN                          | HPS   | VACS |
| Group I                          |                                |                             |                                     |                             |     |     |                              |       |      |                             |     |     |                              |       |      |
| 1                                | 800                            | 460-400                     | 305-375                             | 370                         | 390 | -   | 615                          | < 675 | 610  | 280                         | -   | 340 | -                            | 515   | 460  |
| 2                                | 800                            | 260-210                     | 210-215                             | 200                         | -   | -   | 360                          | < 360 | 360  | 210                         | -   | -   | -                            | 410   | 360  |
| 3                                | 00                             | 340-310                     | 280-395                             | 290                         | -   | -   | 450                          | < 450 | 450  | 230                         | -   | -   | -                            | < 500 | 380  |
| 4                                | 00                             | 360-40                      | 240-290                             | 230                         | -   | -   | 415                          | < 415 | 415  | 210                         | -   | 310 | -                            | 510   | 430  |
| 5                                | 600                            | 290-280                     | 260-310                             | 260                         | 210 | -   | 390                          | < 390 | 390  | 240                         | -   | -   | -                            | 440   | 375  |
| 6                                | 800                            | 470                         | 270                                 | 280                         | 410 | -   | 485                          | < 485 | 485  | 250                         | -   | -   | -                            | 515   | 440  |
| 7                                | 800                            | 410-340                     | 335-465                             | 300                         | -   | -   | 645                          | < 645 | 645  | 250                         | -   | -   | -                            | 460   | 375  |
| 8                                | 00                             | 220-210                     | 180-190                             | 190                         | -   | -   | 340                          | < 340 | 340  | 260                         | -   | -   | -                            | 490   | 430  |
| 9                                | 600                            | 340-290                     | 210-340                             | 280                         | -   | -   | 460                          | < 460 | 460  | 230                         | -   | -   | -                            | 440   | 340  |
| 10                               | 1000                           | 600-310                     | 300-550                             | 300                         | -   | -   | 580                          | < 580 | 580  | 240                         | -   | -   | -                            | < 480 | 380  |
| 11                               | 600                            | 300-290                     | 395-460                             | 260                         | 280 | -   | 430                          | < 430 | 430  | 250                         | 490 | -   | 45                           | 465   | 470  |
| 12                               | 870                            | 460-330                     | 300-400                             | 270                         | 370 | -   | 540                          | < 540 | 540  | 240                         | -   | -   | -                            | 440   | 370  |
| 13                               | 540                            | 390-300                     | 240-90                              | 230                         | -   | -   | 450                          | < 450 | 450  | 210                         | -   | -   | -                            | 395   | 365  |
| Group II                         |                                |                             |                                     |                             |     |     |                              |       |      |                             |     |     |                              |       |      |
| 14                               | 00                             | 410-360                     | 190-220                             | 270                         | 350 | -   | 460                          | < 460 | 460  | 310                         | -   | -   | -                            | -     | 350  |
| 15                               | 700                            | 400-300                     | 200-250                             | 290                         | -   | -   | 450                          | < 450 | 450  | 260                         | -   | -   | -                            | 570   | 275  |
| 16                               | 540                            | 470-250                     | 145-200                             | 210                         | -   | -   | 400                          | < 400 | 400  | 230                         | -   | 260 | -                            | 460   | 270  |
| 17                               | 600                            | 290-230                     | 90-130                              | 220                         | -   | 3.0 | 305                          | < 330 | 330  | 230                         | -   | -   | -                            | 430   | 370  |
| Group III                        |                                |                             |                                     |                             |     |     |                              |       |      |                             |     |     |                              |       |      |
| 18                               | 800                            | 610-40                      | 100-300                             | 230                         | -   | -   | 470                          | < 470 | 470  | 270                         | -   | -   | 45                           | 600   | 445  |
| 19                               | 600                            | 280-230                     | 150-200                             | 220                         | -   | -   | 370                          | < 370 | 370  | 210                         | -   | -   | -                            | < 440 | 370  |
| 20                               | 600                            | 330-60                      | 90-250                              | 220                         | -   | -   | 360                          | < 370 | 370  | 210                         | -   | -   | -                            | 470   | 400  |

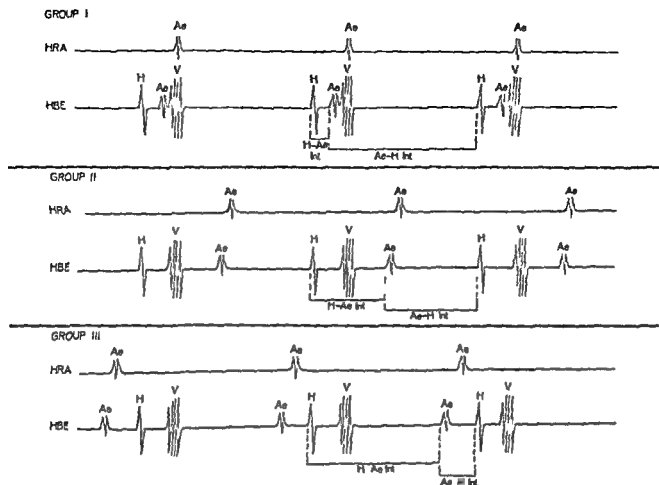
measurements and their ratios were the reverse of Group I. The H-Ae intervals averaged 362.6 msec (range 270 to 470 msec) and the Ae-H intervals were correspondingly short (average 110 msec range 100 to 140 msec) the H-Ae-Ae-H ratios being 1.02-0.4.

The above classification is schematically presented in Fig. 1 and its importance and usefulness will be discussed subsequently.

The characteristic electrophysiological features of the three groups will be presented in greater detail as follows.

**A. Characteristic features of PSVT Group I (patients nos. 1 to 13 Tables I to III)** The most prominent and constant features of PSVT in Group I was the short H-Ae and long Ae-H intervals at all cycle lengths of tachycardia (Fig. 2). The Ae-response (Ret P-wave) was partially or completely obscured by the QRS complex or the initial part of the ST segment. In no patient did the onset of Ae precede the H or follow the end of ventricular electrogram on the HBF. The H-Ae were  $\leq$  H-V intervals in nine out of 13 patients

and exceeded the latter in the remaining four patients (Tables I and III). The H-Ae intervals in Group I remained relatively constant (variations of  $\leq$  5 msec) with changes in cycle length of PSVT. The H-Ae-Ae-H ratios suggested considerably longer Ant conduction times (Ae-H) compared to Ret conduction times (H-Ae). It may be pointed out that since the point of turn around for the reentrant impulse is proximal to the H bundle the H-Ae and Ae-H values do not precisely reflect Ant and Ret A-V nodal conduction times. Changes in the cycle length of PSVT were due to Ae-H interval variation; the H-Ae intervals rarely showed any discernible change. Thus the H-Ae-Ae-H ratio increased at longer and decreased at shorter cycle length of tachycardia. The shortest Ae-H were at least three times longer than H-Ae intervals in the same patient at any given time during PSVT. Spontaneous or vagotonic (carotid sinus pressure etc.) termination of PSVT occurred in the Ant limb of the reentrant circuit (i.e. the Ae was not followed by an H in 11 out of 13 patients (Fig. 2).



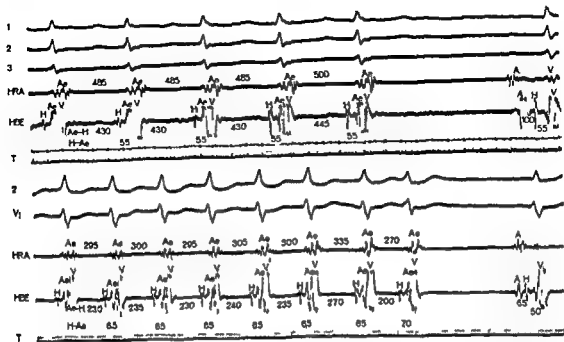
**Fig 1** Schematic presentation of patterns of PSVT. The figure displays in a schematic fashion the II Ae and Ae H relationship during the tachycardia in the three groups. Note the short H Ae and significantly long Ae H intervals in Group I. The H Ae and Ae H intervals in Group II approximate each other whereas in Group III the above relationship is just the opposite of Group I. The figure also demonstrates the manner in which the above intervals were measured. This schema is not representative of the absolute values for any of the given intervals or precise sequence of atrial activation in any of the groups. HRA = high right atrial electrogram recording; HBE = His bundle electrogram recording; H = His bundle deflection; Ae = atrial electro beat; V = local ventricular electrogram; Int = interval. The same abbreviations will be used in subsequent figures.

and in the Ret limb (i.e. no Ae following the H) in one patient (No 11). In the remaining one patient (No 7) termination of PSVT occurred in either the Ant or Ret limb. Termination of PSVT in the Ant limb was preceded by prolongation, shortening or no detectable change in the Ae H interval (Fig 2). In no instance did a PSVT persist when Ant block occurred proximal to the bundle of His (i.e. in the A V node). On the other hand, the development of bundle branch block (seven patients), prolongation in the His Purkinje conduction time (H V interval five patients) or complete block (four patients) within the His Purkinje system (HPS) during a PSVT had no influence on the Ae Ae interval or the H Ae intervals.

When a single atrial premature beat terminated or reinitiated a PSVT in 12 out of 13

patients, single ventricular premature beats terminated the PSVT in only two patients. In the 11 out of 13 patients, single induced ventricular premature beats to the point of ventricular muscle refractoriness had no effect on the Ae Ae cycle.

**Group II (patients Nos 11 to 17, Tables I to III).** A consistent feature during PSVT in Group II was the relatively long H Ae intervals which caused the Ae to occur after the ventricular electrogram on the HBE tracing (Fig 3, panel A). The Ae H intervals were correspondingly short. Group II patients were clearly distinguishable from Group I by the smaller H Ae/Ae H ratios observed in the latter group (Table II). When a change in the cycle length of PSVT with normal intra-ventricular conduction was noted in Group II, the H Ae (and V Ae) intervals



**Fig 2** Pattern of PSVT (Group I). The two tracings taken from patients No 1 (top panel) and No 2 (bottom panel) show the H Ae and Ae H relationship in Group I cases. In the top panel the PSVT terminates with subtle increase in Ae-H interval whereas the H Ae stays constant at 55 msec. The bottom panel shows spontaneous variation in the cycle length of the PSVT primarily from changes in the Ae H intervals. The termination of PSVT is preceded by marked shortening in the Ae-H interval which is associated with only 5 msec increase in the H Ae interval. Note that the onset of Ae on HBE either precedes local V electrogram (top panel) or is obscured by it (bottom panel). In both cases the PSVT terminates in the Ant limb (i.e. no H deflection after the Ae response). Sinus escape beats follow. The A H and H V intervals are labelled. All measurements are in milliseconds. Additional abbreviations: 1, 2, 3 V = ECG leads; T = Time lines recorded at 10 and 100 msec; pts = patients.

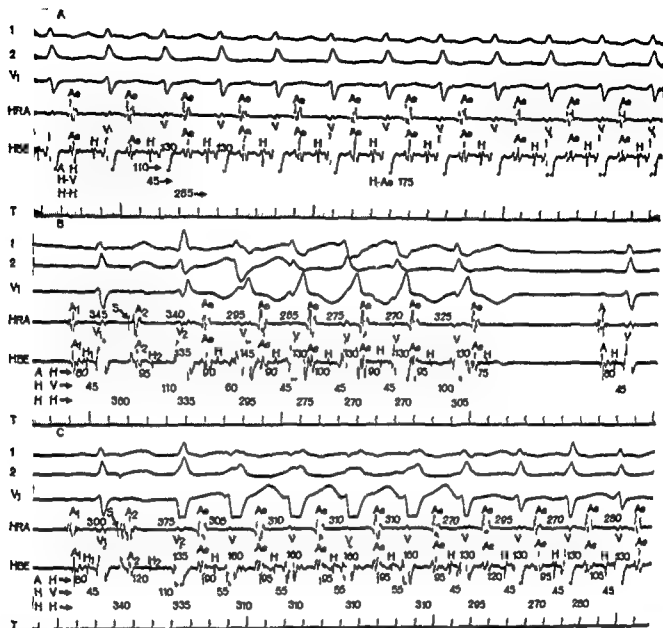
remained constant and a change in the Ae H interval accounted for the variation as seen in Group I patients.

However, unlike Group I, abnormal intraventricular conduction during PSVT had a pronounced influence on the atrial cycle length of tachycardia in Group II cases. In three patients functional bundle branch block resulted in an increase in H Ae interval and consequently the cycle length of PSVT (Ae Ae interval). An H Ae interval prolongation during bundle branch block pattern was due to an increase in the V Ae interval and also the H V interval when the latter coexisted, confirming that the pattern of ventricular muscle activation influenced the subsequent Ae response (Fig 3 panels II and C).

In all Group II cases, PSVT terminated in the Ant limb with block of the Ae proximal to the H in three and distal to the H in the fourth patient (No 7, Fig 3 panel B). Appropriately timed single atrial and ventricular premature beats

terminated or reinitiated the PSVT in all four patients. In three out of four patients single premature ventricular beats induced coincident with or following the H during PSVT resulted in Ret atrial capture (Ar) ahead of the expected Ae response (i.e. the Ae Ar < Ae Ae, Fig 4 panel C). In one patient the premature ventricular beat delivered in the above manner terminated the PSVT without propagation to the atria.

**Group III (patients Nos 18 to 20, Table I to III).** In Group III the H Ae Ae H ratios were the reverse of Group I (Fig 5 panels B and C). A change in the cycle length of the PSVT was due to changes in the H Ae in two and both H Ae and Ae H interval in one patient. Spontaneous termination of PSVT always occurred in the Ret limb (i.e. H was not followed by an Ae (Fig 5 panel C). Aberrant ventricular conduction (seen in two out of three patients) appeared to have no effect on the Ae Ae, the Ae H or H Ae intervals. Single premature atrial beats effectively terminated the PSVT in all patients whereas single premature

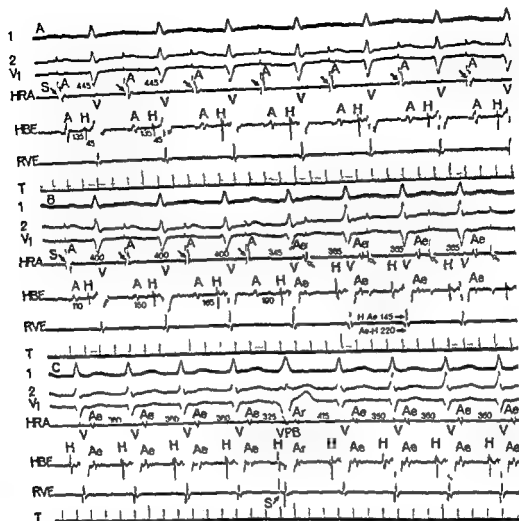


**Fig 3** Pattern of PSVT (Group II Patient No. 17) The tracing shows the H Ae and Ae H relationship during PSVT in Group II during normal (panel A) and aberrant intraventricular conduction (panels B and C). In panel A the cycle length of PSVT (Ae Ae) is 285 msec the H Ae and Ae H intervals measure 175 and 110 msec respectively a ratio of 1.6. The H V and V Ae intervals during normal intraventricular conduction value 45 to 130 msec in that order. Panel B and C show initiation of PSVT with single premature atrial beats (A) coupled to the preceding sinus beats (A). During RBBB (panel B) the V Ae interval is 130 msec (labelled within the V electrogram) and is the same as in panel A whereas during LBBB (panel C) the V Ae is prolonged (160 msec). See how the H V prolongation and intraventricular conduction influence the subsequent Ae. Also when the impulse blocks below the bundle of His (panel B) there is no Ae response. The prolongation in Ae Ae cycle with H V prolongation and during LBBB suggest the reentry via a bypass connected to the left ventricle. It is to be observed that there is no evidence of ventricular pre-excitation during sinus beat (last beat in panel B). Near simultaneous activation of the high and low right atrium during PSVT is also compatible with left sided accessory pathway (i.e. from left ventricle to the left atrium). S = denotes stimulus artifact. RBBB = right bundle branch block. LBBB = left bundle branch block.

ventricular beats terminated the tachycardia in only one.

**B Antegrade and retrograde conduction patterns Group I (patients Nos 1 to 13 Table I)** Incremental atrial pacing produced progressive prolongation in A V nodal conduction (A H inter-

val) and in all patients a PSVT could be initiated during pacing induced Wenckebach phenomenon when critical A H delays were achieved (Fig 6 top panel). The average paced atrial cycle length at the onset of A V nodal Wenckebach phenomenon was 423.4 msec (range 665 to 300 msec). In



**Fig 4** Pattern of PAVT (Group II patient No 16) *Panel A* demonstrates 1:1 A V response at a paced atrial cycle length of 440 msec. The A-H and H-V intervals are 135 and 45 msec respectively. There is no evidence of Ant ventricular pre-excitation. Shortening of the atrial cycle length to 400 msec (*panel B*) results in Ant A V nodal WP. The fourth paced beat is associated with an A-H of 190 msec which initiates the PSVT. The Ae response precedes the next stimulus artifact (white arrow) which is ineffective. The cycle length of PSVT is 345 to 365 msec. The H-Ae and Ae-H intervals are labelled. *Panel C* shows that introduction of a ventricular premature beat (VPB) during stable PSVT which coincides with the Ant His bundle activation results in Ret atrial capture (Ar) ahead of anticipated Ae response i.e.  $Ae-Ar < Ae-Ae$  by 30 msec. The curtailed atrial cycle (Ae-Ar) results in prolongation in the following A-H interval which in turn prolongs the atrial cycle length (Ar-Ae) to 415 msec. The V-Ae remains the same as in panel B. Subsequently the Ae-Ae intervals stabilize at 360 msec. RVE = right ventricular electrogram. WP = Wenckebach phenomenon.

seven out of 13 patients the longest paced atrial cycle length which resulted in A V nodal Wenckebach phenomenon were longer than the atrial cycle length of the PSVT such that the first Ae preceded the next expected paced impulse (Fig 6). In the remaining six patients the atrial cycle length during a PSVT were equal to or greater than the paced atrial cycle length producing A V nodal Wenckebach phenomenon.

In all Group I patients incremental ventricular pacing produced small but definite increases in V-A intervals. At the slowest paced ventricular rates the V-A intervals averaged 137.3 msec (range 115 to 200 msec). The average increase in V-A interval from the longest to the shortest paced ventricular cycle length with 1:1 V-A response was 21.1 msec (range 5 to 70 msec). The V-A intervals prolongation in all probability

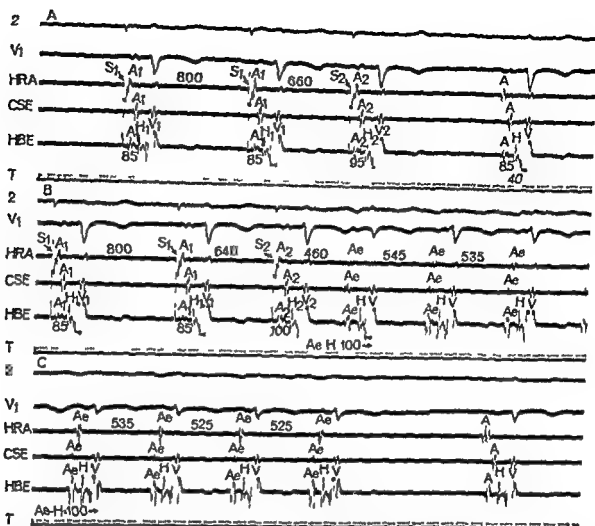


Fig 5 Pattern of PSVT (Group III patient No 18) Panel B demonstrates initiation of PSVT with an atrial coupling interval of 640 msec. The A-H interval in panel B is only slightly longer than the A-H interval of the basic drive beat. The PSVT could not be induced at longer coupling intervals and shorter A-H delays (panel A). Observe the relatively long H-Ae and correspondingly short Ae-H interval (panel B and C). Panel C shows spontaneous termination of the PSVT in the retrograde limb. See text for details. CSE = coronary sinus electrogram.

represented increases in the H-A intervals (Ret A-V nodal conduction time) rather than the V-H interval (Ret HPS conduction time)."

In 11 out of 13 patients a 1:1 V-A response occurred up to maximum paced ventricular rates (average cycle length 355.4 msec) whereas in two patients Ret block occurred at cycle length of 400 and 460 msec respectively. In seven out of 13 patients Ant A-V nodal Wenckebach phenomenon occurred at slower paced rates than did Ret Wenckebach phenomenon (Fig 6). In four out of 13 patients 1:1 A-V and V-A responses occurred up to maximum comparable paced rates. Of the remaining two patients who developed both Ant and Ret Wenckebach phenomenon during incremental pacing in only one patient did the onset of Ret Wenckebach phenomenon occur at a slower rate.

In only two out of 13 patients could a PSVT be initiated during continuous ventricular pacing and in both no prior prolongation in the V-A intervals were noted (Fig 6 bottom panel).

Group II (patients Nos 14 to 17 Table I). In Group II conduction patterns during incremental atrial pacing were similar to Group I. The average atrial cycle length at the onset of Ant A-V nodal Wenckebach phenomenon was 396.2 msec (range 300 to 460 msec). In all four patients a PSVT could be induced when critical degrees of A-H delays were achieved (Fig 4 panels A and B). In two patients the atrial cycle length during PSVT was shorter (Fig 4 panel B) than the paced atrial cycle length which initiated a tachycardia. The opposite was observed in the remaining two patients. Incremental ventricular pacing produced no increases in V-A intervals up

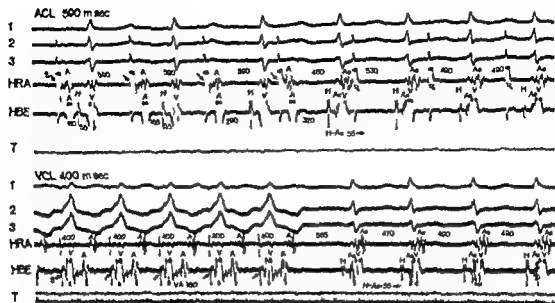


Fig 6 Antegrade and retrograde conduction pattern (Group I patient No 1). The top panel shows Ant-AV nodal Wenckebach cycle at a paced atrial CL of 500 msec. The longest conducted A-H interval of 370 msec results in the initiation of PSVT. The first A-e response precedes the oncoming artificial stimulus which is ineffective (white arrow). The CL of PSVT is significantly shorter than the paced ACL which produced Ant-AV nodal WP. During ventricular pacing (bottom panel) at a CL of 400 msec, 1:1 V-A response occurs; the V-A interval measures 160 msec. When the stimulus is omitted following the fifth paced beat, the PSVT is initiated without prior prolongation in V-A interval. Note that VA conduction system in this patient was capable of sustaining a 1:1 response at faster rates compared to the A-V conduction system. CL = cycle length; ACL = paced atrial cycle length; VCL = paced ventricular cycle length; WP = Wenckebach phenomenon.

to maximum paced rates of 170 to 200 beats/min. The V-A intervals averaged 136.2 msec (range 110 to 160 msec).

In none of Group II patients was a PSVT induced during incremental ventricular pacing.

Group III (patients Nos 18 to 20 Table I). Progressive increases in A-H intervals occurred during incremental atrial pacing. The average paced atrial cycle length at the onset of Ant-AV nodal Wenckebach phenomenon was 348.3 msec (range 315 to 400 msec). In all three patients a PSVT was initiated during incremental atrial pacing. However, the A-H intervals which preceded the onset of PSVT were only slightly longer than those of sinus beats (i.e., 30 to 75 msec > A-H intervals of sinus beats). In all patients the atrial cycle length during a PSVT was longer than the paced atrial cycle length resulting in Ant-AV nodal Wenckebach phenomenon.

The V-A intervals at the longest paced ventricular cycle length averaged 150 msec (range 140 to 160 msec). The average increase in V-A from

slowest to the fastest paced ventricular rates with 1:1 V-A response was 21.6 msec (range 10 to 30 msec). In one patient Ret-Wenckebach phenomenon occurred at slower paced rates than did the Ant-counterpart and in the remaining two patients 1:1 A-V and V-A responses were observed up to the maximum paced rates. In one out of three patients was a PSVT initiated during progressive prolongation in V-A intervals produced by ventricular pacing.

C. Antegrade and retrograde refractory periods. Table III lists for the three groups of patients the pertinent refractory period data obtained at comparable atrial and ventricular paced cycle lengths (i.e., A-A or V-V).

Group I. Antegrade refractory period studies. Within a critical range of A-A intervals and A-H<sub>1</sub> delays, A<sub>2</sub> always resulted in PSVT (Fig 7). The longest A-A<sub>2</sub> and shortest A-H<sub>1</sub> intervals which initiated PSVT had mean values of 381.5 ± 93.5 and 276.2 ± 55.3 msec, respectively. The critical range of A-H<sub>1</sub> delays were comparable to the critical A-H intervals which produced PSVT.



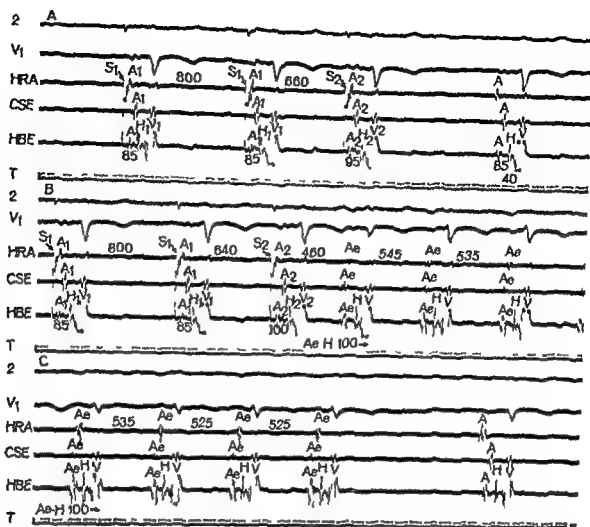


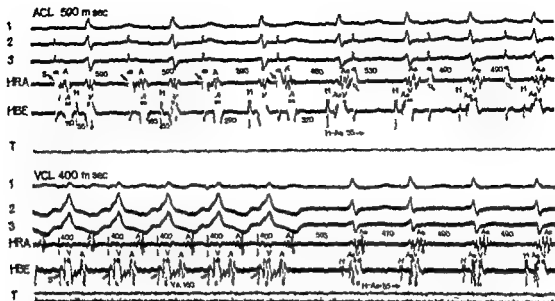
Fig 5 Pattern of PSVT (Group III patient No 18) Panel B demonstrates initiation of PSVT with an atrial coupling interval of 640 msec. The A-H interval in panel B is only slightly longer than the A-H interval of the basic drive beat. The PSVT could not be induced at longer coupling intervals and shorter A-H delays (panel A). Observe the relatively long H-Ae and correspondingly short Ae-H interval (panel B and C). Panel C shows spontaneous termination of the PSVT in the retrograde limb. See text for details. CSE = coronary sinus electrogram.

represented increases in the H-A intervals (Ret A-V nodal conduction time) rather than the V-H interval (Ret HPS conduction time).<sup>11</sup>

In 11 out of 13 patients a 1:1 V-A response occurred up to maximum paced ventricular rates (average cycle length 355.4 msec) whereas in two patients Ret block occurred at cycle length of 400 and 460 msec respectively. In seven out of 13 patients Ant A-V nodal Wenckebach phenomenon occurred at slower paced rates than did Ret Wenckebach phenomenon (Fig 6). In four out of 13 patients 1:1 A-V and V-A responses occurred up to maximum comparable paced rates. Of the remaining two patients who developed both Ant and Ret Wenckebach phenomenon during incremental pacing in only one patient did the onset of Ret Wenckebach phenomenon occur at a slower rate.

In only two out of 13 patients could a PSVT be initiated during continuous ventricular pacing and in both no prior prolongation in the V-A intervals were noted (Fig 11 bottom panel).

**Group II (patients Nos 14 to 17 Table I)** In Group II conduction patterns during incremental atrial pacing were similar to Group I. The average atrial cycle length at the onset of Ant A-V nodal Wenckebach phenomenon was 196.2 msec (range 300 to 460 msec). In all four patients a PSVT could be induced when critical degrees of A-H delays were achieved (Fig 4 panels A and B). In two patients the atrial cycle length during PSVT was shorter (Fig 4 panel B) than the paced atrial cycle length which initiated a tachycardia. The opposite was observed in the remaining two patients. Incremental ventricular pacing produced no increases in V-A intervals up



**Fig 6** Antegrade and retrograde conduction pattern (Group I patient No. 1) The top panel shows Ant AV nodal Wenckebach cycle at a paced atrial CL of 550 msec. The longest conducted A-H interval of 370 msec results in the initiation of PSVT. The first A-CL response precedes the oncoming artificial stimulus which is ineffective (white arrow). The CL of PSVT is significantly shorter than the paced ACL which produced Ant AV nodal WP. During ventricular pacing (bottom panel) at a CL of 400 msec 1:1 V-A response occurs. The V-A interval measures 160 msec. When the stimulus is omitted following the fifth paced beat the PSVT is initiated without prior prolongation in V-A interval. Note that VA conduction system in this patient was capable of sustaining a 1:1 response at faster rates compared to the AV conduction system. CL = cycle length, ACL = paced atrial cycle length, VCL = paced ventricular cycle length, WP = Wenckebach phenomenon.

to maximum paced rates of 170 to 200 beats/min. The V-A intervals averaged 136.2 msec (range 110 to 160 msec).

In none of Group II patients was a PSVT induced during incremental ventricular pacing.

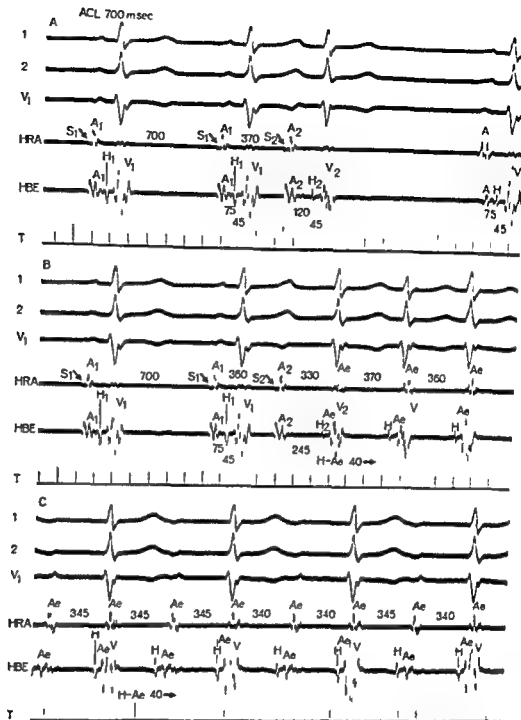
**Group III (patients Nos 18 to 20 Table 1)**  
Progressive increases in AH intervals occurred during incremental atrial pacing. The average paced atrial cycle length at the onset of Ant A V nodal Wenckebach phenomenon was 348.3 msec (range 315 to 400 msec). In all three patients a PSVT was initiated during incremental atrial pacing. However the AH intervals which preceded the onset of PSVT were only slightly longer than those of sinus beats (i.e. 10 to 75 msec  $>$  AH intervals of sinus beats). In all patients the atrial cycle length during a PSVT was longer than the paced atrial cycle length resulting in Ant A V nodal Wenckebach phenomenon.

The  $\frac{1}{2}$  A intervals at the longest paced ventricular cycle length averaged 150 msec (range 140 to 160 msec). The average increase in  $\frac{1}{2}$  A from

slowest to the fastest paced ventricular rates with 1:1 V A response was 216 msec (range 10 to 30 msec). In one patient Ret Wenckebach phenomenon occurred at slower paced rates than did the Ant. counterpart and in the remaining two patients 1:1 A V and V A responses were observed up to the maximum paced rates. In one out of three patients was a PSVT initiated during progressive prolongation in V A intervals produced by ventricular pacing.

C Antegrade and retrograde refractory periods Table III lists for the three groups of patients the pertinent refractory period data obtained at comparable atrial and ventricular paced cycle lengths (i.e. A<sub>1</sub>A or VV)

**Group I Antegrade refractory period studies**  
Within a critical range of A A<sub>1</sub> intervals and A<sub>1</sub>H<sub>1</sub> delays A<sub>1</sub> always resulted in PSVT (Fig 7). The longest A A<sub>1</sub> and shortest A<sub>1</sub>H<sub>1</sub> intervals which initiated PSVT had mean values of  $381.5 \pm 93.5$  and  $276.2 \pm 55.3$  msec respectively. The critical range of A H delays were comparable to the critical A H intervals which produced PSVT.



**Fig 7** Antegrade refractory period pattern (Group I patient No 4) At a basic atrial cycle length of 700 an A-A of 370 msec A conducts with an A-H of 120 and an H-V of 45 msec respectively. The resulting H-H interval was the shortest obtainable at this CL and measures 415 msec (FRP A-V node). Since no prolongation in H-V interval was noted during premature beat the H-H equal V-V such that the FRP of the A-V CS is determined by the A-V node. Panel B shows initiation of PSVT at closer A-A interval of 360 msec. Sudden prolongation of A-H interval occurs and coincides with beginning of the PSVT. Discontinuous FRI curves were noted in this patient (ref 7). The typical H-Ae and Ae-H relationship of Group I patients is obvious. An episode of 2:1 block within the HEPs is shown in panel C during PSVT and it should be noted that the H-Ae and Ae-H relationship remains the same as in panel B. The onset of Ae on HBE is clearly identifiable when there is no accompanying local ventricular electrogram (panel C).

during incremental atrial pacing. In ten out of thirteen patients the atrial cycle length during incremental pacing which resulted in PSVT exceeded the A-A<sub>1</sub> intervals which initiated the tachycardia. The antegrade refractory period

(ERP) of the A-V node was longer than atrial ERP in five patients whereas the latter exceeded the former in the remaining eight patients. Neither Ae nor PSVT were noted when A<sub>1</sub> blocked proximal to the bundle of His.

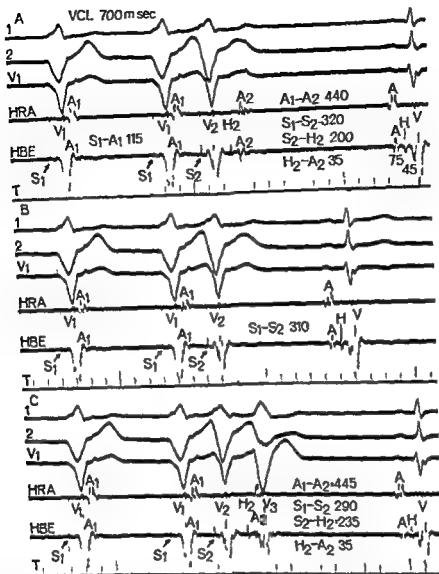
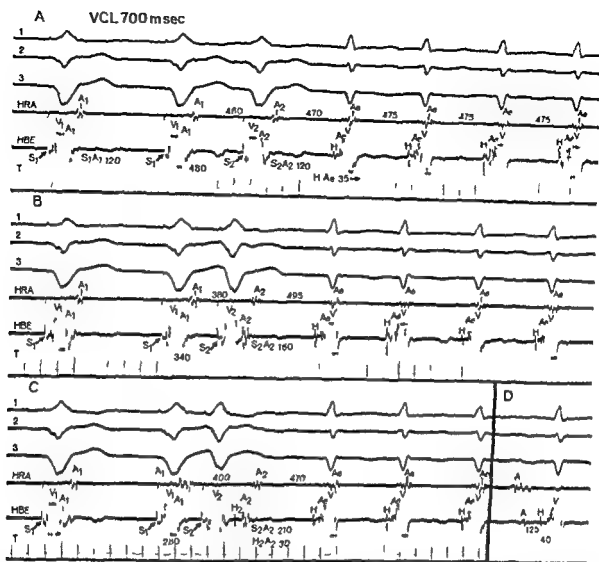


Fig 8 Retrograde refractory period pattern (Group I patient No. 4). The basic ventricular cycle length (S-S) is constant at 700 msec in all panels. The retrograde His bundle deflection during the basic drive is obscured by the local ventricular electrogram. At an S-S interval of 320 msec (panel A) the S conducts to the atria with S-H (Ret His-Purkinje conduction time) of 200 msec and an H-A (Ret. A-V nodal conduction time) of 35 msec. A sinus escape beat follows. At a closer S-S of 310 msec (panel B) S blocks below the bundle of His. Further decrease in S-S interval (panel C) results in resumption of V-A conduction and V is followed by another reentrant ventricular beat (V) from reentry within the HPS. The V fails to retrogradely depolarize the atria (i.e., no A) by virtue of its block below the bundle of His. Note that the H<sub>2</sub>A intervals in panels A and C measure the same and the shortest A-A (FRP V-A-C, panel A) is determined primarily by the HPS. Also evident is the fact that PSVT was not initiated during premature ventricular stimulation either by V or V<sub>2</sub>.

During Ant. refractory period studies the functional refractory period (FRP) of the A-V node exceeded the FRP of RP and relative refractory period of the HPS. Therefore the FRP of the atrioventricular conduction system (AVCS) was determined by the A-V node in all patients (i.e. shortest H-H, equalled the shortest V-V intervals

[Fig 7 top panel]). Three patients (Nos 4, 12 and 14) demonstrated discontinuous curves during refractory period measurements similar to those described previously.

**Retrograde refractory period studies.** During Ret. refractory period determinations the HPS had the longest ERP in two patients the



**Fig 9** Retrograde refractory period pattern (Group I patient No. 10). The figure demonstrates initiation of PSVT at a basic ventricular cycle length of 700 msec and at decreasing S-S intervals (Panels A to C). In panel A the PSVT starts at an S-S of 480 msec without any discernible prolongation in the V-A interval (ie S-A = S-V). The PSVT could be initiated at all shorter S-S intervals. Panel C demonstrates emergence of H from V. Note the relatively short H-A interval of 30 msec. Panel D shows a reference sinus beat.

A V node in one patient and the ventricular muscle in ten patients. The FRP of the ventriculoatrial conduction system (VACS) was determined by the HPS in 12 out of 13 patients (ie Ret delay was only encountered below the bundle of His Fig 8) and the A-V node in one patient. The FRP of the AVCS was significantly longer than that of the VACS in Group I (FRP AVCS  $478 \pm 104.0$  msec, FRP VACS  $393.4 \pm 34.7$  msec,  $p$  value  $< 0.025$ ).

In five out of 13 patients the induced premature ventricular beat (V) was followed by a reentrant beat (V) resulting from reentry within the HPS. In none of these patients did V, conduct to the atria nor did V, initiate a PSVT (Fig 8 bottom panel). In only one patient from Group I did V initiate the PSVT (Fig 9).

During Ret refractory period studies the Ret

H bundle deflection during the basic drive (H<sub>1</sub>) was obscured by the ventricular electrogram. However at closer V-V intervals the Ret H emerged from V, in all patients. In 12 out of 13 patients the H-A<sub>1</sub> intervals were noted to remain constant at decreasing V-V intervals. The H-A<sub>1</sub> intervals (as measured from the end of H<sub>1</sub> to the onset of A<sub>1</sub>) in Group I patients averaged 47.7 msec (range 25 to 80 msec). An attempt was made to compare the Ret H-A with H-A<sub>1</sub> interval measured from comparable points: ie from the end of H during Ret and from the onset of H during Ant depolarization of the His bundle. Since the H-A intervals were determined during refractory period studies and were preceded by longer intervals compared to the cycle length of PSVT (ie the Ret H-H<sub>1</sub> were  $>$  H-H cycle of PSVT) the H-A intervals were not directly

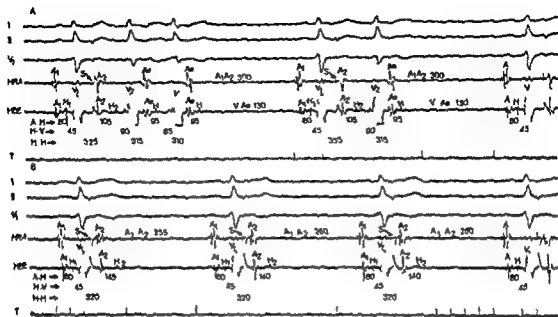


Fig 10 Initiation and spontaneous termination of PSVT (Group II patient No 17) Premature atrial beats (A) are coupled to preceding sinus beats (A). Initiation of PSVT is shown in panel A where A conducts with A-H of 105 msec and H-V of 80 msec. Note the spontaneous termination of tachycardia when the impulse antegradely blocks below the bundle of His. The A-H interval of the last two beats in the first episode (panel A) measures the same and the A-e response only occurs when the reentrant impulse activates the ventricles. This is clearly shown also in panel B where A-H delays are longer compared to panel A; however in the absence of ventricular activation the PSVT is not initiated.

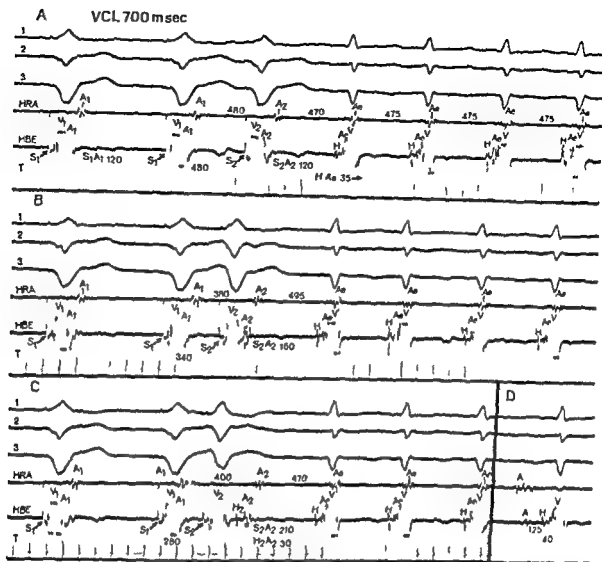
comparable to the H-Ae intervals and therefore the H-A intervals were corrected for the rate of PSVT in the following manner. Since the H-A intervals during slow ventricular paced rates were equal to or less than H-A intervals in any given patient the increment of H-A intervals from the slow ventricular rates to the ventricular rates similar to the rate of PSVT were added to the H-A values. These correct H-A values so obtained cannot be considered precise but should only slightly exceed if at all the true H-A intervals if the latter could be directly measured. When the corrected H-A intervals were compared to the H-Ae intervals the former exceeded the latter by an average of 20 msec (range 1 to 70 msec) or less in Group I patients.

**Group II Antegrade refractory period studies**  
The critical A-A intervals which induced PSVT in Group II were similar to group I ( $351 \pm 915$  msec for Group I vs  $341 \pm 60$  msec for Group II) but the minimum A-H intervals necessary to initiate a PSVT were considerably shorter for Group II cases ( $161 \pm 418$  vs  $276 \pm 53$  msec,  $p$  value < 0.01) since ventricular muscle appeared to be essential for the occurrence

of PSVT in these patients it is obvious that the critical intervals were the AV (i.e. A-H + H-V) rather than A-H intervals. In three out of four patients the A-H prolongation was not accompanied by H-V<sub>1</sub> prolongation and therefore increases in A-V<sub>1</sub> intervals paralleled that of the A-H intervals. However in one patient who did demonstrate H-V<sub>1</sub> prolongation during atrial premature stimulation it could be directly documented that the initiation of PSVT required critical A-V rather than A-H delays (Fig 10).

In one patient the A-V node and in one patient the HPS had the longest ERP during Ant. refractory period studies. In the remaining two patients the atrial ERP exceeded the FRP of the A-V node and the HPS. The FRP of the AVCS was determined by the A-V node in three patients and by the HPS in one patient.

**Retrograde refractory period studies** During Ret. refractory period studies V-A<sub>1</sub> equalled the V-A at decreasing V-V<sub>1</sub> intervals. At closer coupling intervals when H emerged from the ventricular electrogram the Ret. A<sub>1</sub> preceded H<sub>1</sub> (Figs 11 and 12) suggesting conduction via an



**Fig 9** Retrograde refractory period pattern (Group I patient No 10) The figure demonstrates initiation of I SVT at a basic ventricular cycle length of 700 msec and at decreasing SS intervals (Panel A to C) In panel A the PSVT starts at an SS<sub>1</sub> of 480 msec without any discernible prolongation in the V<sub>1</sub> interval ie  $SA_1 = SA_2$  The PSVT could be initiated at all shorter SS intervals Panel C demonstrates emergence of I<sub>1</sub> from V<sub>1</sub> Note the relatively short I<sub>1</sub>A interval of 30 msec Panel D shows a reference sinus beat

A V node in one patient and the ventricular muscle in ten patients. The FRP of the ventriculo atrial conduction system (VACS) was determined by the HPS in 12 out of 13 patients (i.e. Ret. delay was only encountered below the bundle of His, Fig. 8) and the A V node in one patient. The FRP of the AVCS was significantly longer than that of the VACS in Group I (FRP AVCS  $478 \pm 104.0$  msec, FRP VACS  $393.4 \pm 34.7$  msec,  $p$  value  $< 0.025$ ).

In five out of 13 patients the induced premature ventricular beat ( $V_1$ ) was followed by a reentrant beat ( $V_2$ ) resulting from reentry within the HPS. In none of these patients did  $V_1$  conduct to the atria nor did  $V_1$  or  $V_2$  initiate a PSVT (Fig 8 bottom panel). In only one patient from Group I did  $V_2$  initiate the PSVT (Fig 9).

During Ret refractory period studies the Ret

H bundle deflection during the basic drive ( $H_1$ ) was obscured by the ventricular electrogram. However at closer  $V_1V_1$  intervals the Ret H emerged from  $V_1$  in all patients. In 12 out of 13 patients the  $H A_2$  intervals were noted to remain constant at decreasing  $V_1V_1$  intervals. The  $H A_1$  intervals (as measured from the end of H to the onset of  $A_1$ ) in Group I patients averaged 47.7 msec (range 23 to 80 msec). An attempt was made to compare the Ret  $H A_1$  with  $H A_1$  interval measured from comparable points, i.e. from the end of H during Ret and from the onset of H during Ant depolarization of the His bundle. Since the  $H A_1$  intervals were determined during refractory period studies and were preceded by longer intervals compared to the cycle length of PSVT (i.e. the Ret  $H_1H_2$  were  $> H_1$  cycle of PSVT) the  $H A_1$  intervals were not directly

which A antegradely conducted over the normal pathway to initiate a PSVT (Fig 12). When V failed to activate the atria (A<sub>1</sub>) the PSVT did not occur (one out of three patients (Fig 11 top panel)).

**Group III Antegrade refractory period studies** The echo and PSVT zone in Group III was quite comparable to the other two groups. However the shortest AH delays which produced PSVT in Group III were significantly shorter (Fig 5 panels A and B) than in Group I patients ( $113.3 \pm 32.1$  msec vs  $276.2 \pm 3$  msec,  $p$  value  $< 0.001$ ). No statistically significant difference existed between Group II and III patients when the above comparisons were made. The atrial muscle had the longest ERP in all three patients and the FRP of the AVCS was determined by the A-V node in two patients and the HPS in one patient.

**Retrograde refractory period studies** During Ret refractory period studies the FRP of the ventricular muscle exceeded that of the A-V node and HPS in all three patients.

The FRP of the AVCS was determined by the A-V node in one patient and the HPS in the other two patients. The mean value for the FRP of the AVCS as  $421.6 \pm 114$  and AVCS  $383.3 \pm 23$  msec; the differences however were statistically insignificant.

The PSVT could be initiated with a single ventricular premature beat in only one patient. The ventricular premature beats that initiated PSVT were associated with V A<sub>1</sub> intervals that were longer than V A intervals.

For the entire group of 20 patients the mean value for the atrial ERP exceeded that of the ventricular ERP but no significant difference was noted. Similarly there was no significant difference between the atrial and ventricular ERP between the three groups.

## Discussion

It is apparent from the present study and previous reports that the site of reentry in patients with PSVT in the absence of ventricular pre-excitation is variable and an attempt should be made to delineate the reentrant circuits in individual patients. The present data indicates that in Group I patients (which constituted the majority) the most likely site of reentry was the A-V node whereas in Group II patients a Ret A-V of the Kent bundle type was utilized by the reentrant impulse during PSVT.

In Group III patients although a limited number of observations were available it was possible to exclude the utilization of a Ret AP during PSVT. Whether the site of reentry in Group III patients was the A-V node or the low atria will be discussed subsequently.

It is important to emphasize that certain electrophysiological findings were of no help in determining the site of reentry in this series of patients. These include resting ECG P-R intervals, cycle length of PSVT, initiation of PSVT with single premature atrial beats or during Ant A-V nodal Wenckebach phenomenon. The role of those electrophysiologic parameters which allowed localization of the reentrant pathways along with their limitation are discussed below.

**1 Effect of abnormal intraventricular conduction on cycle length of PSVT.** A change in cycle length of PSVT during a change in intraventricular conduction suggests reentry via an AP. Since ventricular muscle activation is an essential link in the reentrant circuit in such cases (Group II) both H-V prolongation and ipsilateral bundle branch block (on the side of AP connection) during PSVT will prolong the H-Ae and V-Ae intervals (Fig 3). The Ae-Ae prolongation at times however is followed by a significantly shorter Ae-H interval and if such a conduction pattern stabilizes the cycle length of PSVT during aberrant conduction may in fact be shorter than during normal intraventricular conduction. The reverse may occur when abnormal intraventricular conduction converts to normal conduction during a PSVT retrogradely utilizing an AP. The sudden decrease in Ae-Ae cycle may either result in Ae-H prolongation and consequent increase in the atrial cycle length of PSVT (Fig 13) or the Ae may block antegradely and terminate the PSVT. It is important therefore that Ae-Ae intervals be analyzed at the transition in intraventricular conduction since during established normal or abnormal intraventricular conduction the cycle length of PSVT may be the same even though the H-Ae intervals stay longer during aberrant ventricular conduction.

**2 Effect of single ventricular premature beats on cycle length of PSVT.** During PSVT if single ventricular premature beats induced coincident with or following the Ant H result in termination of PSVT or in Ret atrial capture (Ar) sooner than the expected Ae reentry via a Ret AP is strongly suggested. The above criterion is still



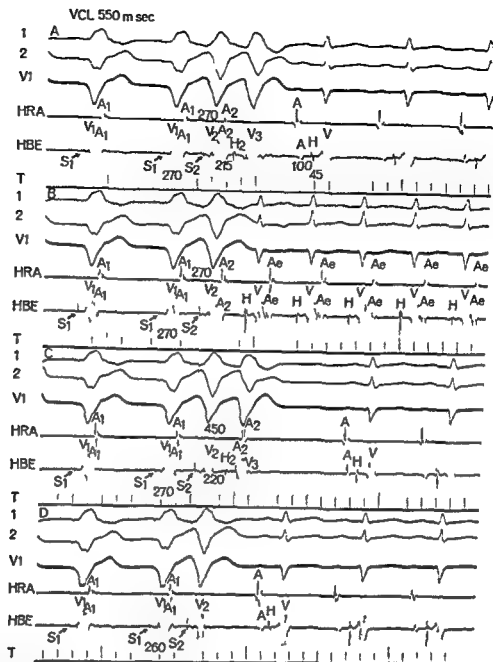


Fig 11 Retrograde refractory period pattern in PSVT (Group II patient No 16) In all panels the basic ventricular cycle length is the same. In panel A  $S_1$  conducts retrogradely with an S-A interval which equals to S-A such that the A-A = S-S. The  $S_1$  also conducts to the bundle of His with an S-H interval of 215 msec. Another ventricular beat from reentry in the HPS ( $V_1$ ) follows. The fact that the A<sub>1</sub> precedes H suggests that atrial activation occurred via an accessory pathway not connected to the bundle of His (Kent bundle).  $V_1$  blocks retrogradely in both pathways and a sinus beat follows. In panel B the  $S_1$  retrogradely blocks below the bundle of His (no H) however  $S_1$  conducts to the atria (A) via the accessory pathway. A in turn conducts antegradely via the normal pathway and the PSVT is initiated. In panel C the  $S_1$  blocks retrogradely in the accessory pathway and conducts via the normal pathway (H precedes A). The  $V_1$  response occurs from S-H delay similar to the one seen in panel A. The S-S intervals in panels A to C are the same. At a shorter coupling interval of 200 msec (panel D)  $S_1$  blocks retrogradely in both pathways (no H or A). The shortest A-A intervals were achieved by conduction via a Kent bundle silent antegradely (see the sinus beats and compare with those during PSVT) so that the FRP of the VACS was determined by refractoriness of the bypass tract.

accessory pathway not in direct continuity with the bundle of His. In only one patient did the Ret ERP of the accessory pathway (AP) exceed that of the ventricular muscle (Fig 11) whereas in the remaining three patients the Ret ERP of the AP was less than that of the ventricular muscle. The FRP of the VACS in Group II (which was

determined by the AP) was significantly shorter than FRP of the AVCS ( $p$  value  $< 0.001$ ). In three out of four patients closer  $V_1$  intervals resulted in  $V_1$  from reentry in the HPS. In two out of three patients  $V_1$  retrogradely blocked below the bundle of His (ie no H) while conducting to the atria (A) via the AP following

which A antegradely conducted over the normal pathway to initiate a PSVT (Fig 12) = When V<sub>1</sub> failed to activate the atria (A<sub>1</sub>) the PSVT did not occur (one out of three patients (Fig 11 top panel))

**Group III Antegrade refractory period studies** The echo and PSVT zone in Group III was quite comparable to the other two groups. However the shortest A<sub>1</sub>H<sub>1</sub> delays which produced PSVT in Group III were significantly shorter (Fig 5 panels A and B) than in Group I patients ( $113.3 \pm 32.1$  msec vs  $276.2 \pm 3$  msec,  $p$  value  $< 0.001$ ). No statistically significant difference existed between Group II and III patients when the above comparisons were made. The atrial muscle had the longest ERP in all three patients and the FRP of the AVCS was determined by the A V node in two patients and the HPS in one patient.

**Retrograde refractory period studies** During Ret refractory period studies the ERP of the ventricular muscle exceeded that of the A V node and HPS in all three patients.

The FRP of the AVCS was determined by the A V node in one patient and the HPS in the other two patients. The mean value for the FRP of the AVCS was  $421.6 \pm 114$  and AVCS  $383.3 \pm 23$  msec; the differences however were statistically insignificant.

The PSVT could be initiated with a single ventricular premature beat in only one patient. The ventricular premature beats that initiated PSVT were associated with V A<sub>1</sub> intervals that were longer than V A intervals.

For the entire group of 20 patients the mean value for the atrial ERP exceeded that of the ventricular FRP but no significant difference was noted. Similarly there was no significant difference between the atrial and ventricular ERP between the three groups.

## Discussion

It is apparent from the present study and previous reports that the site of reentry in patients with PSVT in the absence of ventricular pre-excitation is variable and an attempt should be made to delineate the reentrant circuits in individual patients. The present data indicates that in Group I patients (which constituted the majority) the most likely site of reentry was the A V node whereas in Group II patients a Ret AP of the Kent bundle type was utilized by the reentrant impulse during PSVT.

In Group III patients although a limited number of observations were available it was possible to exclude the utilization of a Ret AP during PSVT. Whether the site of reentry in Group III patients was the A V node or the low atria will be discussed subsequently.

It is important to emphasize that certain electrophysiological findings were of no help in determining the site of reentry in this series of patients. These include resting ECG P R intervals, cycle length of PSVT, initiation of PSVT with single premature atrial beats or during Ant A V nodal Wenckebach phenomenon. The role of those electrophysiologic parameters which allowed localization of the reentrant pathways along with their limitation are discussed below.

**1 Effect of abnormal intraventricular conduction on cycle length of PSVT** A change in cycle length of PSVT during a change in intraventricular conduction suggests reentry via an AP. Since ventricular muscle activation is an essential link in the reentrant circuit in such cases (Group II) both H V prolongation and ipsilateral bundle branch block (on the side of AP connection) during PSVT will prolong the H Ae and V Ae intervals (Fig 3). The Ae Ae prolongation at times however is followed by a significantly shorter Ae-H interval and if such a conduction pattern stabilizes the cycle length of PSVT during aberrant conduction may in fact be shorter than during normal intraventricular conduction. The reverse may occur when abnormal intraventricular conduction converts to normal conduction during a PSVT retrogradely utilizing an AP. The sudden decrease in Ae Ae cycle may either result in Ae H prolongation and consequent increase in the atrial cycle length of PSVT (Fig 13) or the Ae may block antegradely and terminate the PSVT. It is important therefore that Ae Ae intervals be analyzed at the transition in intraventricular conduction since during established normal or abnormal intraventricular conduction the cycle length of PSVT may be the same even though the H Ae intervals stay longer during aberrant ventricular conduction.

**2 Effect of single ventricular premature beats on cycle length of PSVT** During PSVT if single ventricular premature beats induced coincident with or following the Ant H result in termination of PSVT or in Ret atrial capture (Ar) sooner than the expected Ae reentry via a Ret AP is strongly suggested. The above criterion is still

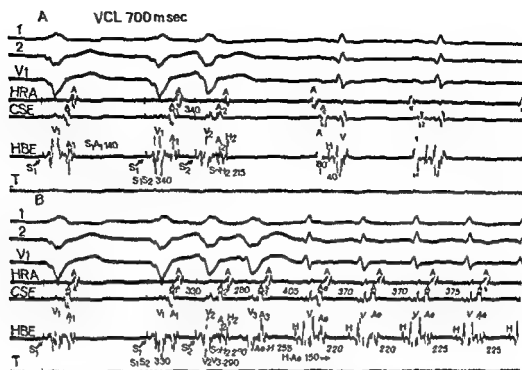


Fig 12 Retrograde refractory period pattern (Group II patient No 15) At a basic ventricular cycle length of 700 msec and an S-H of 340 msec (Panel A) A response occurs via an accessory pathway S also conducts to the bundle of His with an S-H of 215 msec Note the absence of ventricular pre-excitation during sinus beat At shorter S-H, and longer S-H delay (panel B) V<sub>1</sub> is followed by another ventricular beat (V<sub>2</sub>) from reentry within the JPS V<sub>1</sub> in turn activates the atria (A) via the anomalous pathway and at the same time blocks below the bundle of His A finds the normal pathway recovered sufficiently and antegradely conducts to start the tachycardia

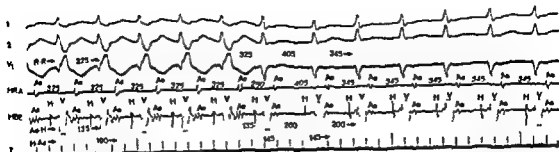
valid if the induced beat precedes the Ant H by an interval less than the H V intervals of sinus beats since the V H interval (during right ventricular apical pacing) almost always exceeds the H V interval. However if the premature ventricular beat precedes the Ant H by more than the H V interval of sinus beats, then it is theoretically possible to engage the Ret limb of an A V nodal reentry circuit which will make it difficult to determine whether the reentry is occurring within the A V node or via an AP. It was however noted in this study that single ventricular premature beats rarely had any effect in Group I and III patients whereas the PSVT was uniformly terminated in Group II patients. The lack of effect of single premature ventricular beats may be due to either (a) that the reentry circuits in Groups I and III were located farther away from the site of stimulation (i.e. the A V node or atrium) and/or (b) the premature ventricular beats blocked retrogradely below the bundle of His which will obviously have no effect upon the reentry in or above the A V node but could still engage a Kent bundle.

3 Antegrade and retrograde conduction ratios during PSVT. A relatively simple and reproducible finding which suggested the site of reentry was the H Ae and Ae H relationship. Neither the

H Ae intervals nor the H Ae Ae H showed any overlap of values between the three groups in this series of patients.

In Group I in whom the site of reentry was the A V node the Ae had a constant relationship with the H over a wide range of PSVT rates and the Ae never preceded the H or followed the end of ventricular electrogram in HBE recording. If functional and/or anatomic duality of A V nodal pathways is the basis of reentry in these patients then it is conceivable that Ant block in one pathway with prolonged conduction (A H interval) in the other pathway may allow good conduction in the Ret limb of reentry circuit and account for the short H Ae intervals. The short H Ae in turn will be followed by longer Ae H interval and if such a conduction is stabilized the pattern of Group I PSVT will emerge. Theoretically conduction in Ant and Ret limbs of A V nodal reentry circuit could balance such that the H Ae and Ae H intervals may approximate each other (pattern of Group II) or the H Ae may exceed the Ae H interval (pattern of Group III). This however did not occur in any of the patients in Group I at any time.

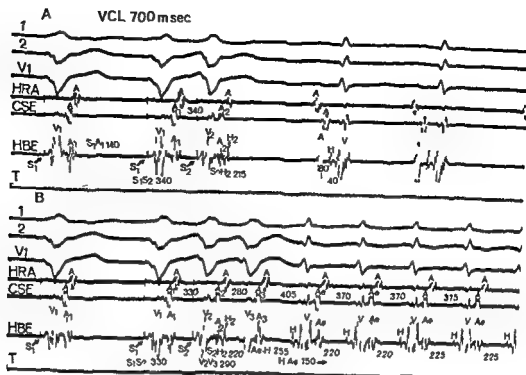
The presence of relatively longer H Ae intervals during PSVT in Group II patients was not surprising since the H Ae intervals included



**Fig. 13** Intraventricular conduction and rate of PSVT (Group II patient No. 16) The cycle length of PSVT is usually stable at 325 msec during aberrant intraventricular conduction of the right bundle branch block type. The Ae H and H Ae intervals measure 135 and 190 msec respectively. With the conversion of intraventricular conduction to normal (sixth QRS complex) there is sudden decrease in H Ae interval to 145 msec which results in corresponding shortening of the Ae Ae interval. The decrease in the Ae Ae cycle length to 280 msec results in significant prolongation in the following Ae H interval which measures 260 msec and by virtue of which both Ae Ae and R R intervals increase to a value of 405 msec. Subsequently the conduction stabilizes such that the cycle length of PSVT during normal QRS complex is longer than during aberrant QRS complexes. The H V interval throughout the episode of PSVT is the same (i.e., 45 msec) and therefore the decrease in the H Ae during normal intraventricular conduction is entirely accounted for by a decrease in V Ae interval which suggests a right sided ventriculoatrial bypass connection.

conduction times (1) in the HPS (the H V interval) (2) from the onset of ventricular activation to the Ret penetration of the AP (3) within the AP and (4) to the atrium in the vicinity of HBE recording site. It is to be noted that since most anomalous connection of the Kent bundle type are located around the base of the heart (i.e. A V ring) a significant amount of time may elapse between the ventricle activation via the normal pathway and Ret penetration of the AP. This is probably true for both patients with or without evidence of Ant. ventricular pre excitation (the delta wave). One can argue that if an atrial recording was made in closer proximity to the atrial end of the AP the H Ae (where the Ae is recorded from an atrial site close to the AP) will be shorter. Although this is true the Ae as recorded on the HBF usually occurs late enough to be clearly separated from the ventricular electrogram regardless of the atrial and ventricular end of the bypass insertion. Patients with septal connections may have shorter H Ae and V Ae intervals compared to those with more lateral connection. However the H Ae and Ae H interval relationship presented here for Group II cases appears to be the rule rather than the exception in patients with WPW syndrome in whom reentry via a bypass was documented with epicardial mapping technique. The ratios presented in Table II were obtained during normal intraventricular conduction and it goes without saying that abnormal intraventricular conduction during PSVT in these cases may significantly change these ratios.

In group III patients the PSVT was initiated at relatively shorter A-H intervals compared to Group I patients and H-Ae intervals were correspondingly longer. Although reentry via an AP was excluded, the exact site of reentry was difficult to determine in Group III patients due to a limited number of observations available. The reversal of H-Ae-Ae-H may conceivably reflect reversal of conduction balance or direction of conduction in the Ant and Ret limb of A-V nodal reentry circuit as compared to Group I. The ability to induce tachycardia with relatively small increases in A-H intervals on the other hand suggests that the A-H delays may have no direct bearing on the initiation of PSVT and the site of reentry may be above the A-V node perhaps in the low atria. Intra atrial reentry in the region of the sinus node is a fairly well documented phenomenon in man<sup>21</sup> and conceivably such a process can also occur in other parts of the atria.<sup>22</sup> If the sequence of atrial activation during an intra atrial reentrant tachycardia is from low to high the distinction between A-V nodal reentry and intra atrial reentry may be difficult to make. The ability to initiate Group III PSVT at minimal A-H delays and the lack of correlation between Ret conduction and patterns of conduction during PSVT in these patients makes intra atrial reentry a distinct possibility. Reentry in the low atria cannot be entirely excluded for Group I cases. However the facts that (1) reentry was related to critical A-H delays rather than atrial coupling intervals and (2) in five out of 13 patients in Group I when A blocked



**Fig 12** Retrograde refractory period pattern (Group II patient No 15) At a basic ventricular cycle length of 700 msec and an S<sub>1</sub>S<sub>2</sub> of 340 msec (Panel A) A<sub>1</sub> response occurs via an accessory pathway & also conducts to the bundle of His with an S<sub>1</sub>H<sub>1</sub> of 215 msec Note the absence of ventricular pre-excitation during sinus beat At shorter S<sub>1</sub>S<sub>2</sub> and longer S<sub>1</sub>H<sub>1</sub> delay (panel B) V<sub>1</sub> is followed by another ventricular beat (V<sub>2</sub>) from reentry within the HPS V<sub>2</sub> in turn activates the atria (A<sub>2</sub>) via the anomalous pathway and at the same time blocks below the bundle of His A<sub>2</sub> finds the normal pathway recovered sufficiently and antegradely conducts to start the tachycardia

valid if the induced beat precedes the Ant H by an interval less than the H V intervals of sinus beats since the V H interval (during right ventricular apical pacing) almost always exceeds the H V interval.<sup>12</sup> However, if the premature ventricular beat precedes the Ant H by more than the H V interval of sinus beats then it is theoretically possible to engage the Ret limb of an A V nodal reentry circuit which will make it difficult to determine whether the reentry is occurring within the A V node or via an AP. It was however noted in this study that single ventricular premature beats rarely had any effect in Group I and III patients whereas the PSVT was uniformly terminated in Group II patients. The lack of effect of single premature ventricular beats may be due to either (a) that the reentry circuits in Groups I and III were located farther away from the site of stimulation (i.e. the A V node or atrium) and/or (b) the premature ventricular beats blocked retrogradely below the bundle of His which will obviously have no effect upon the reentry in or above the A V node but could still engage a Kent bundle.

**3 Antegrade and retrograde conduction ratios during PSVT** A relatively simple and reproducible finding which suggested the site of reentry was the H Ae and Ae H relationship. Neither the

H Ae intervals nor the H Ae Ae H showed any overlap of values between the three groups in this series of patients.

In Group I in whom the site of reentry was the A V node, the Ae had a constant relationship with the H over a wide range of PSVT rates and the Ae never preceded the H or followed the end of ventricular electrogram in HBE recording. If functional and/or anatomic duality of A V nodal pathways is the basis of reentry in these patients then it is conceivable that Ant block in one pathway with prolonged conduction (A H interval) in the other pathway may allow good conduction in the Ret limb of reentry circuit and account for the short H Ae intervals. The short H Ae in turn will be followed by longer Ae H interval and if such a conduction is stabilized the pattern of Group I PSVT will emerge. Theoretically conduction in Ant and Ret limbs of A V nodal reentry circuit could balance such that the H Ae and Ae H intervals may approximate each other (pattern of Group II) or the H Ae may exceed the Ae H interval (pattern of Group III). This however did not occur in any of the patients in Group I at any time.

The presence of relatively longer H Ae intervals during PSVT in Group II patients was not surprising since the H Ae intervals included

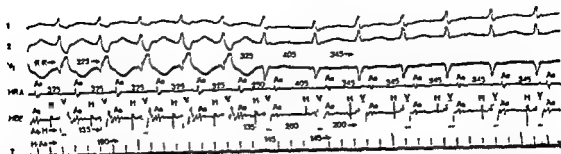


Fig. 13 Intraventricular conduction and rate of PSVT (Group II patient No. 16). The cycle length of PSVT is initially stable at 323 msec during aberrant intraventricular conduction of the right bundle branch block type. The Ae-H and H-Ae intervals measure 130 and 190 msec respectively. With the conversion of intraventricular conduction to normal (sixth QRS complex) there is sudden decrease in H-Ae interval to 145 msec which results in corresponding shortening of the Ae-Ae interval. The decrease in the Ae-Ae cycle length to 250 msec. results in significant prolongation in the following Ae-H interval which measures 400 msec., and by virtue of which both Ae-Ae and R-R intervals increase to a value of 400 msec. Subsequently the conduction stabilizes, such that the cycle length of PSVT during normal QRS complex is longer than during aberrant QRS complexes. The H-V interval throughout the episode of PSVT is the same (i.e., 40 msec) and therefore the decrease in the H-Ae during normal intraventricular conduction is entirely accounted for by a decrease in V-Ae interval which suggests a right sided ventriculoatrial bypass connection.

conduction times (1) in the HPS (the H-V interval) (2) from the onset of ventricular activation to the Ret penetration of the AP (3) within the AP and (4) to the atrium in the vicinity of HBE recording site. It is to be noted that since most anomalous connection of the Kent bundle type are located around the base of the heart (i.e. A-V ring) a significant amount of time may elapse between the ventricle activation via the normal pathway and Ret penetration of the AP. This is probably true for both patients with or without evidence of Ant. ventricular pre-excitation (the delta wave). One can argue that if an atrial recording was made in closer proximity to the atrial end of the AP the H-Ae (where the Ae is recorded from an atrial site close to the AP) will be shorter. Although this is true the Ae as recorded on the HBE usually occurs late enough to be clearly separated from the ventricular electrogram regardless of the atrial and ventricular end of the bypass insertion. Patients with septal connections may have shorter H-Ae and V-Ae intervals compared to those with more lateral connection. However the H-Ae and Ae-H interval relationship presented here for Group II cases appears to be the rule rather than the exception in patients with WPW syndrome in whom reentry via a bypass was documented with epicardial mapping technique. The ratios presented in Table II were obtained during normal intraventricular conduction and it goes without saying that abnormal intraventricular conduction during PSVT in these cases may significantly change these ratios.

In group III patients the PSVT was initiated at relatively shorter A-H<sub>1</sub> intervals compared to Group I patients and H-Ae intervals were correspondingly longer. Although reentry via an AP was excluded the exact site of reentry was difficult to determine in Group III patients due to limited number of observations available. The reversal of H-Ae-Ae-H may conceivably reflect reversal of conduction balance or direction of conduction in the Ant and Ret limb of A-V nodal reentry circuit as compared to Group I. The ability to induce tachycardia with relatively small increases in A-H intervals on the other hand suggests that the A-H delays may have no direct bearing on the initiation of PSVT and the site of reentry may be above the A-V node perhaps in the low atria. Intra atrial reentry in the region of the sinus node is a fairly well documented phenomenon in man and conceivably such a process can also occur in other parts of the atria.<sup>12</sup> If the sequence of atrial activation during an intra atrial reentrant tachycardia is from low to-high the distinction between A-V nodal reentry and intra atrial reentry may be difficult to make. The ability to initiate Group III PSVT at minimal A-H<sub>1</sub> delays and the lack of correlation between Ret conduction and patterns of conduction during PSVT in these patients makes intra atrial reentry a distinct possibility. Reentry in the low atria cannot be entirely excluded for Group I cases. However the facts that (1) reentry was related to critical A-H delays rather than atrial coupling intervals and (2) in five out of 13 patients in Group I when A blocked

proximal to the His bundle the PSVT could not be initiated even at closer A<sub>1</sub>A<sub>2</sub> intervals argue against intra atrial reentrant process

Although good correlation existed between the site of reentry and H Ae and Ae H ratios in the present series of patients a clear cut distinction may not be always possible. However, the presence of such a relationship in any patient should alert one to the possible sites of reentry which can then be confirmed or excluded with various electrophysiologic interventions mentioned above

**Role of A V nodal bypass tracts in PSVT**  
Although Ret conduction during PSVT and ventricular pacing in Group I patients occurred via the same pathway it is not certain whether the Ret conduction occurred via the A V node or a partial A V nodal bypass tract.<sup>23</sup> In a similar manner the pattern of PSVT seen in Group III may represent Ant conduction via a partial A V nodal bypass tract and Ret conduction through the A V node. The presence or absence of such partial A V nodal bypass tracts and their role in PSVT is not certain at this writing

From the results of this study one can reasonably exclude the utilization of complete A V nodal bypass tracts for Ret conduction since in all Group I patients the Ret H A intervals corrected from the rate of PSVT exceeded the H Ae intervals. The two intervals will be expected to be the same if the AP completely bypassed the A V node and directly inserted into the bundle of His. Since the H A intervals were only slightly longer than H Ae intervals (by  $\geq 20$  msec on the average) it appears that the point of turn around (crossover fibers) was probably located in the distal portion of the A V node (i.e., the NH region)

**Significance of better V A conduction in patients with PSVT**  
The majority of patients in Groups I and II had better V A than A V conduction 10 out of 17 patients) i.e. 1:1 V A response was maintained at faster paced rates compared to the A V response.<sup>24</sup> In six out of 17 patients a 1:1 response occurred in both directions up to maximum comparable paced rates and in only one out of 17 patients was the A V conduction better than V A conduction. In Group III the A V conduction was either better than V A conduction (one out of 13 patients) or conduction in both directions was equal

The existence of good V A conduction in Group II patients is not surprising and is comparable to

patients with Wolff Parkinson White syndrome.<sup>25</sup> If it is assumed that Group I patients utilize A V node for a Ret conduction then the presence of better V A conduction in this group is a unique and interesting finding since the majority of the patients without PSVT have better A V conduction.<sup>26</sup> If Ret conduction in Group I did indeed occur across the A V node it is obvious that these patients had remarkably good and rapid Ret A V nodal conduction (i.e. H A interval). These observations suggest that the presence of relatively good Ret conduction displayed by Group I cases might make them prone to PSVT

In the majority of Group I patients the AVCS maintained a 1:1 A V response at faster rates during PSVT compared to the paced atrial rates. This indicates that either the reentrant impulse short circuited a portion of the A V node (in which case the atrium was not an essential link in the reentry circuit), or the Ae penetrated the A V node from a different site compared to the paced atrial impulse bypassing the more refractory areas of the A V node. Such a difference in A V nodal response from different sites of pacing has been previously demonstrated.<sup>27</sup> Perhaps one or both mechanisms mentioned above are operative in different patients

No such conclusions as drawn above for Groups I and II could be drawn for Group III since no consistent relationship existed between the pattern of PSVT and Ret conduction

An extremely important observation was the presence of intact V A conduction in all patients in this series. The absence of V A conduction (Ret A V nodal block) is a relatively common finding in patients without PSVT.<sup>28</sup> It is doubtful if a reentrant process (both via A V node and AP) can ever occur in the absence of V A conduction. The existence of atrial tachycardia in patients without V A conduction should alert one to the possibility of intra atrial reentry or ectopic atrial automaticity

**Role of A H delays in initiating PSVT**  
Although PSVT was initiated at certain A H delays in all patients their role was different in the three groups. In Group I the A V nodal conduction was essential for the reentrant process to manifest itself. In Group II the degree of A H delay was relevant to the extent it produced A V prolongation. For Group III cases the PSVT could be induced at shortest A H intervals and as pointed out above the role of such delays in

initiating the reentrant process is not certain. If it is possible to induce atrial automaticity with atrial stimulation then this additional possibility must also be considered as a possible mechanism of tachycardia in Group III patients.<sup>23</sup>

**Patterns of refractory periods** The Ant refractory period studies per se were not of much help in determining the site of reentry in the three groups. However the Ret refractory period studies as well as the comparison between the Ant and Ret refractory periods provided a great deal of new information as follows.

In Group I patients A V node determined the FRP of the AVCS in all patients. In the same group HPS determined the FRP of the VACS in 12 out of 13 patients. Since the Ant refractoriness (of the A V node) exceeded the Ret refractoriness (of the HPS) the FRP of the AVCS significantly exceeded the FRP of the VACS. This is in direct contrast to the findings in other subjects without PSVT in whom the FRP of the VACS generally exceeds that of the AVCS.<sup>1</sup> The above findings also explain why the PSVT in Group I generally terminated in the Ant limb i.e. Ae blocked in the A V node.

The pathway utilized for Ret conduction in Group I patients in addition to good conduction also had shorter refractoriness than that of the HPS. These findings have important electrophysiologic implications. It is generally accepted that A V nodal reentry represents functional duality of the pathways having different refractory period and conduction velocities. When Ant block is induced in the fast conducting pathway (with longer refractoriness) conduction occurs exclusively via the slow pathway (with shorter refractoriness).<sup>24</sup> If the conduction delay along the slow pathway is sufficient the impulse can cross over and engage the fast pathway for Ret propagation to initiate a PSVT. The so called "fast pathway" however did not demonstrate any evidence of longer refractoriness during Ret conduction or refractory period studies. In addition the slow pathway was never used exclusively for Ret conduction and hence appeared to have longer refractoriness than the fast pathway. The significance of these findings and their relationship to Ant conduction patterns remains uncertain at this writing.

The Ret refractory period pattern in Group II was quite similar to patients with Wolff Parkinson White syndrome. A point of caution is that unless the Ret ERP of the bypass is less than the

A V node and the HPS one may not be able to demonstrate presence of a bypass during ventricular premature stimulation even though the bypass tract is used during PSVT.

The longer refractoriness of the AVCS relative to the VACS explains the termination of PSVT in the Ant limb in all the Group II cases.

In Group III the FRP of the VACS exceeded that of the AVCS. The PSVT in these patients uniformly terminated in the Ret limb which suggests that the refractoriness of the Ret limb was longer than the Ant limb if the process was A V nodal reentry. On the other hand if intra atrial reentry or ectopic atrial automaticity were the mechanisms of PSVT in these patients it is easy to explain why the Ae did not follow an H when the intra atrial reentrant or ectopic process was terminated.

### Summary

In 20 patients with PSVT without ventricular pre excitation the site of reentry and functional characteristics of Ant and Ret pathways were studied. Three distinct patterns of PSVT were observed. In 13 patients (group I) in whom A V node was the site of reentry the interval between the Ant H bundle deflection and the following atrial echo response (H Ae) measured 30 to 85 msec and the Ae was partially or completely obscured by ventricular electrogram. The ratio between the H Ae and the subsequent Ae H interval ranged 1.31 to 1.73. In a majority of Group I patients (eight out of 13) the Ret conduction was better than Ant conduction as the VACS sustained a 1:1 response at faster paced rates than AVCS. The FRP of the AVCS in Group I was determined by the A V node in all patients and significantly exceeded the FRP of the VACS; the latter was determined by the HPS in 12 out of 13 patients. In four patients (Group II) a V A AP silent antegradely was operative during PSVT. The H Ae in Group II valued 145 to 200 msec and the Ae clearly followed the ventricular electrogram the H Ae Ae H being 1.05 to 1.7. The V A conduction in all Group II patients was better than the A V conduction. A V node determined the FRP of the AVCS whereas AP determined the FRP of the VACS in Group II patients and the former significantly exceeded the latter. Good correlation existed between PSVT Ant and Ret conduction patterns in Group I and Group II patients.

In three patients (Group III) the H Ae



measured 270 to 470 msec with an H A e A e H of 1 0 2 0 4 a relationship quite the opposite of Group I patients. No definite relationship existed between PSVT Ant and Ret conduction patterns in Group III patients. The data in Group III patients were compatible with (1) A V nodal reentry with reversal of conduction balance compared to Group I, (2) intra atrial reentry, and (3) enhanced atrial automaticity.

It is concluded (1) the site of reentry in patients with PSVT is variable (2) a fair estimation of reentry site can be made from H A e and A e H relationship (3) all patients with PSVT have intact V A conduction and in most the V A conduction is better than A V conduction, and (4) in the majority of patients with PSVT refractoriness of the AVCS exceeds that of the VACS.

## REFERENCES

- Bigger J T Jr and Goldreyer B N The mechanism of supraventricular tachycardia. *Circulation* 42:673 1970
- Goldreyer B N and Bigger J T Jr Site of reentry in paroxysmal supraventricular tachycardia in man. *Circulation* 43:35 1971
- Spurrell R A J and Sowton E Study of mechanism and treatment of supraventricular tachycardia using His bundle electrograms. *Br Heart J* 34:962 1972
- Goldreyer B N and Damato A N The essential role of A V conduction delay in the initiation of paroxysmal supraventricular tachycardia in man. *Circulation* 43:14 1971
- Spurrell R A J, Ankler D and Sowton E Two or more intra A V nodal pathways in association with either a James or Kent extra nodal bypass in 3 patients with paroxysmal supraventricular tachycardia. *Br Heart J* 35:113 1973
- Denes P, Wyndham C R C, Wu D and Rosen K M Supernormal conduction of a premature impulse utilizing the fast pathway in a patient with dual A V nodal pathways. *Circulation* 51:811 1975
- Denes P, Wu D, Dingra R C, Chuquimia R and Rosen K M Demonstration of dual A V nodal pathways with paroxysmal supraventricular tachycardia. *Circulation* 48:549 1973
- Wu D, Denes P, Wyndham C, Amat, Leon F, Dingra R C and Rosen K M Demonstration of dual atrioventricular nodal pathways utilizing a ventricular extrastimulus in patients with atrioventricular nodal reentrant paroxysmal supraventricular tachycardia. *Circulation* 52:769 1975
- Spurrell R A J, Ankler D M and Sowton F Concealed bypasses of the atrioventricular node in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. *Am J Cardiol* 33:390 1974
- Neuss H, Schlepper M and Thormann J Analysis of reentry mechanisms in three patients with concealed Wolff Parkinson White syndrome. *Circulation* 51:3 1975
- Wellens H J J and Durrer D The role of an accessory atrioventricular pathway in reciprocating tachycardia. Observations in patients with and without the Wolff Parkinson White syndrome. *Circulation* 52:53 1975
- Akhtar M, Damato A N, Batsford W I, Ruskin J N and Ogunkelu J H and Vargas G R Demonstration of reentry within the His-Purkinje system in man. *Circulation* 50:1150 1974
- Akhtar M, Damato A N, Batsford W I, Ruskin J N and Ogunkelu J H A comparative analysis of antegrade and retrograde conduction in man. *Circulation* 52:766 1975
- Coumel P H, Waynberger M Les tachycardies par rythme réciproque au cours du syndrome de W P W. *Physiopathologie et traitement. Coeur Med Inter* 11: 1972
- Coumel P H and Attuel P Reciprocating tachycardia in overt and latent pre-excitation. Influence of functional bundle branch block on the rate of the tachycardia. *Eur J Cardiol* 1:423 1974
- Zipes D P, De Joseph R L and Rothbaum M A Unusual properties of accessory pathway. *Circulation* 49:1200 1974
- Wellens H J J and Durrer D Patterns of ventriculo-atrial conduction in the Wolff Parkinson White syndrome. *Circulation* 49:22 1974
- Svenson R H, Miller H C, Gallagher J J and Wallace A G Electrophysiological evaluation of the Wolff Parkinson White syndrome. Problems in assessing antegrade and retrograde conduction over the accessory pathway. *Circulation* 52:552 1975
- Tonkin A M, Dugan F A, Svenson R H, Sealy W C, Wallace A G and Gallagher J J Coexistence of functional Kent and Mahaim type tracts in the pre-excitation syndrome. Demonstration by catheter techniques and epicardial mapping. *Circulation* 52:191 1975
- Gallagher J J, Gilbert M, Svenson R H, Miller H, Sealy W C, Kasell J and Wallace A C Wolff Parkinson White syndrome. The problem evaluation and surgical treatment. *Circulation* 51:6 1975
- Wexler C M, Batsford W I, Taulay K L, Josephson M F, Ogunkelu J B, Akhtar M, Seides S F, Damato A N Sinus node reentrant tachycardia in man. *Am Heart J* 90:29, 1975
- Wu D, Amat, Leon F, Denes, I, Dingra R C, Pietras R J and Rosen K M Demonstration of sustained sinus and atrial reentry as a mechanism of paroxysmal supraventricular tachycardia. *Circulation* 51:234 1975
- James T N The connecting pathways between the sinus node and A V node and between the right and left atrium in the human heart. *Am Heart J* 67:44 1963
- Batsford W P, Akhtar M, Caracci A R, Josephson M D, Seides S F, and Damato A N Effect of atrial stimulation site on the electrophysiological properties of the atrioventricular node in man. *Circulation* 50:743 1974
- Cranefield F E, Aronson R S Initiation of sustained rhythmic activity by single propagated action potentials in canine cardiac Purkinje fibers exposed to sodium free solution or to ouabain. *Circ Res* 34:4 1974
- Mendez C and Moe G K Demonstration of a dual A V nodal conduction system in the isolated rabbit heart. *Circ Res* 18:574 1964

## A possible role of noradrenaline in the development of myocardial infarction

An experimental study in the isolated rat heart

Anders P. Waldenström

Ake C. Hjalmarson

Lars Thornell

Citeborg and Umeå, Sweden

The concept that acute myocardial infarction is caused by coronary artery thrombosis or occlusion has been the subject of considerable debate during recent years. Some studies on autopsy material<sup>1</sup> imply that the coronary thrombosis is the cause of myocardial infarction while other studies show that the coronary artery thrombosis is a secondary phenomenon. The same conclusion is drawn by Friberg and co-workers who have studied the incorporation of <sup>125</sup>I labelled fibrinogen into the coronary thrombosis of patients suffering from myocardial infarction.

Ischemia may be defined as an imbalance between the metabolic demand of a tissue and its supply of oxygen fluid and substrates. It is well known that elevation of sympathetic activity will cause increase in the myocardial energy demand. Ischemia may develop which has been shown to result in local release of noradrenaline. The present investigation uses an *in vitro* perfusion technique to study the deleterious effects of circulating and endogenous noradrenaline as demonstrated by the leakage of creatine phosphokinase (CK) from the myocardium depressed

tissue concentrations of creatine phosphate and ATP and ultrastructural changes. The effects of pretreatment with a beta blocker (*metoprolol*) a calcium antagonist (*verapamil*) or a membrane stabilizer (*lidocaine*) in preventing the detrimental effects of noradrenaline have also been studied. It is suggested that the release of myocardial noradrenaline may play an important role in the myocardial infarction process.

### Material and methods

**Perfusion procedure** Male Wistar rats weighing 350 to 450 Gm and fed a standard pellet diet and water *ad libitum* were heparinized (25 mg intraperitoneally) 30 minutes prior to pentobarbital anesthesia (60 mg/kg of body weight intraperitoneally). The hearts were quickly excised and immersed in ice chilled isotonic saline. As soon as the heart had stopped beating it was mounted in the perfusion apparatus by cannulating the aorta and left atrium. The working rat heart perfusion technique described by Neely and co-workers had been modified by Waldenström and Hjalmarson to permit retrograde perfusion of the hearts with constant perfusion pressure and recirculating buffer. The hearts were perfused with 90 ml of recirculating Krebs-Henseleit bicarbonate buffer (pH 7.4) with glucose (14 mM) and ascorbic acid (0.1 mg/ml) added. The buffer was continuously gassed with 95 per cent O<sub>2</sub> and 5 per cent CO<sub>2</sub>, equilibrated with H<sub>2</sub>O at 37°C. The atrial filling pressure was 10 cm H<sub>2</sub>O and the hearts worked against a hydrostatic pressure of 80 cm H<sub>2</sub>O.

All hearts were initially perfused according to

measured 270 to 470 msec with an H A e A e H of 102.04, a relationship quite the opposite of Group I patients. No definite relationship existed between PSVT Ant and Ret conduction patterns in Group III patients. The data in Group III patients were compatible with (1) A V nodal reentry with reversal of conduction balance compared to Group I, (2) intra atrial reentry, and (3) enhanced atrial automaticity.

It is concluded (1) the site of reentry in patients with PSVT is variable (2) a fair estimation of reentry site can be made from H A e and A e H relationship (3) all patients with PSVT have intact V A conduction and in most the V A conduction is better than A V conduction and (4) in the majority of patients with PSVT refractoriness of the AVCS exceeds that of the VACS.

## REFERENCES

- Bigger J T Jr and Goldreyer B N. The mechanism of supraventricular tachycardia. *Circulation* 42:673, 1970.
- Goldreyer B N and Bigger J T Jr. Site of reentry in paroxysmal supraventricular tachycardia in man. *Circulation* 43:15, 1971.
- Spurrell R A J and Sowton E. Study of mechanism and treatment of supraventricular tachycardia using His bundle electrograms. *Br Heart J* 34:962, 1972.
- Goldreyer B N and Damato A N. The essential role of A V conduction delay in the initiation of paroxysmal supraventricular tachycardia in man. *Circulation* 43:14, 1971.
- Spurrell R A J, Krikler D and Sowton E. Two or more intra A V nodal pathways in association with either a James or Kent extra nodal bypass in 3 patients with paroxysmal supraventricular tachycardia. *Br Heart J* 35:113, 1973.
- Denes P, Wyndham C R C, Wu D and Rosen K M. Supernormal conduction of a premature impulse utilizing the fast pathway in a patient with dual A V nodal pathway. *Circulation* 51:811, 1975.
- Denes P, Wu D, Dhingra R C, Chughumia R and Rosen K M. Demonstration of dual A V nodal pathways with paroxysmal supraventricular tachycardia. *Circulation* 48:49, 1973.
- Wu D, Denes P, Wyndham C, Amat-Lyon F, Dhingra R C and Rosen K M. Demonstration of dual atrioventricular nodal pathways utilizing a ventricular extrastimulus in patients with atrioventricular nodal reentrant paroxysmal supraventricular tachycardia. *Circulation* 52:789, 1975.
- Spurrell R A J, Krikler D M and Sowton E. Concealed bypasses of the atrioventricular node in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. *Am J Cardiol* 33:970, 1974.
- Neus H, Schlippner M and Thormann J. Analysis of reentry mechanisms in three patients with concealed Wolff Parkinson White syndrome. *Circulation* 51:75, 1975.
- Wellens H J J and Durrer D. The role of an accessory atrioventricular pathway in reciprocating tachycardia. Observations in patients with and without the Wolff Parkinson White syndrome. *Circulation* 52:58, 1975.
- Akhtar M, Damato A N, Batford W P, Ruskin J N, Ogunkelu J B and Vargas G R. Demonstration of reentry within the His Purkinje system in man. *Circulation* 50:1150, 1974.
- Akhtar M, Damato A N, Batford W P, Ruskin J N and Ogunkelu J B. A comparative analysis of antegrade and retrograde conduction in man. *Circulation* 52:766, 1975.
- Coumel P, H. Waynberger M. Les tachycardies par rythme réciproque au cours d'un syndrome de W P W. *Physiopathologie et traitement*. *Coeur Med Inter* 11:7, 1972.
- Coumel P H and Attuel P. Reciprocating tachycardia in overt and latent pre-excitation. Influence of functional bundle branch block on the rate of the tachycardia. *Fur J Cardiol* 1:423, 1974.
- Zipes D P, De Joseph H L and Rothbaum D A. Unusual properties of accessory pathway. *Circulation* 49:1200, 1974.
- Wellens H J J and Durrer D. Patterns of ventriculo-atrial conduction in the Wolff Parkinson White syndrome. *Circulation* 49:22, 1974.
- Svenson R H, Miller H C, Gallagher J J and Wallace A G. Electrophysiological evaluation of the Wolff Parkinson White syndrome. Problems in assessing antegrade and retrograde conduction over the accessory pathway. *Circulation* 52:552, 1975.
- Tonkin A M, Dugan F A, Sven R H, Sethi W C, Wallace A G and Gallagher J J. Co-existence of functional Kent and Mahaim type tracts in the pre-excitation syndrome. Demonstration by catheter techniques and epicardial mapping. *Circulation* 52:191, 1975.
- Gallagher J J, Gilbert M, Svenson R H, Miller H, Sethi W C, Kasell J and Wallace A C. Wolff Parkinson White syndrome. The problem evaluation and surgical treatment. *Circulation* 51:76, 1975.
- Weisfogel C M, Batford W P, Faulstich K I, Josephson M E, Ogunkelu J B, Akhtar M, Seides S F, Damato A N. Sinus node reentrant tachycardia in man. *Am Heart J* 90:293, 1975.
- Wu D, Amat-Lyon F, Denes P, Dhingra R C, Lefkowitz R I and Rosen K M. Demonstration of sustained sinus and atrial reentry as a mechanism of paroxysmal supraventricular tachycardia. *Circulation* 51:231, 1975.
- James T N. The connecting pathways between the sinus node and A V node and between the right and left atrium in the human heart. *Am Heart J* 67:418, 1963.
- Batford W P, Akhtar M, Caracci A R, Josephson M D, Seides S F and Damato A N. Effect of atrial stimulation site on the electrophysiological properties of the atrioventricular node in man. *Circulation* 50:281, 1974.
- Cranefield J F, Aronson R S. Initiation of sustained rhythmic activity by a single propagated action potential in canine cardiac Purkinje fibers exposed to calcium free solution or to ouabain. *Circ Res* 34:4, 1974.
- Mendez C and Moe G K. Demonstration of a dual A V nodal conduction system in the isolated rabbit heart. *Circ Res* 19:378, 1967.

followed by perfusion with buffer containing glutaraldehyde (2.5 per cent) for 15 minutes at  $+4^{\circ}\text{C}$ . The hearts were then fixed in the glutaraldehyde solution for an additional 6 hours. After fixation the hearts were rinsed in Tyrode's solution while slices of about 1 mm were cut from the midregion of the ventricles. From these slices the free left ventricular wall was subdivided into five groups of tissue blocks of 1 mm<sup>3</sup> so that each group of blocks represented successive layers of the myocardium from the endocardium to the epicardium. The blocks were postfixed in 1 per cent osmium tetroxide in Tyrode's solution for 2 hours, rinsed in buffer, dehydrated in graded series of acetone and finally embedded in Vestopal W. Ultrathin slices were cut in a LKB Ultratome and the slices were collected on formvar coated keyhole or meshgrid stained with uranyl acetate and lead citrate before examination in a Philips EM 300 Electron Microscope.

### Statistics

Comparisons between means were performed with the Student's *t* test. A *p* value  $\leq 0.05$  was considered significant in this study.

### Results

#### Effects of endogenous noradrenaline

**Coronary and aortic flow.** There was no change in coronary flow caused by the addition of noradrenaline to the perfusion medium in concentrations of  $10^{-7}\text{M}$  to  $10^{-5}\text{M}$  (Table 1). On the other hand there was a decrease in aortic flow at concentrations of  $10^{-6}\text{M}$  or greater.

**Myocardial content of ATP and creatine phosphate.** Hearts perfused for 45 minutes with noradrenaline had lower contents of ATP but an accumulation of creatine phosphate with increasing noradrenaline concentrations in the buffer (Fig. 1).

**Release of ASAT and CK to the perfusion medium.** There was a leakage of ASAT and CK from well perfused hearts when noradrenaline was added to the perfusion buffer (Fig. 2). A dose response relationship between the concentration of noradrenaline and the leakage of enzymes was demonstrated. A concentration of  $10^{-6}\text{M}$  of noradrenaline did not cause a greater leakage of ASAT or CK than in controls. At a concentration

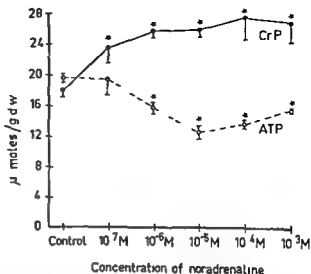


Fig. 1 Effects of different concentrations of noradrenaline on myocardial ATP and creatine phosphate (CrP). The hearts were perfused anterogradely for 15 minutes and retrogradely for 30 minutes. Each value represents the mean  $\pm$  SE for 6 to 8 hearts. \* = significantly different from the control ( $p < 0.05$ ).

of  $10^{-6}\text{M}$  of noradrenaline however there was a significant leakage of both enzymes which was further increased by  $10^{-5}\text{M}$  of noradrenaline. Addition of  $10^{-3}\text{M}$  however did not cause any further increase in leakage. The increases in the activities of ASAT and CK became statistically significant after 25 minutes of perfusion when perfused with noradrenaline  $10^{-6}\text{M}$  to  $10^{-3}\text{M}$ .

**Changes in myocardial ultrastructure.** Ultrastructural lesions were seen in the myocardium of hearts perfused with noradrenaline. Damaged muscle fibers were scattered throughout the myocardium without any preferential location. At low concentrations of noradrenaline ( $10^{-7}\text{M}$ ) the myocardial lesions consisted mainly of single affected myocardial fibers surrounded by perfectly normal cells. At higher concentrations of noradrenaline the number of damaged cells was increased and clusters of affected cells were seen. The capillaries always appeared to be open and had a normal ultrastructure (Fig. 3). The morphology of the affected cells was highly variable however with regard to the characteristics of the lesions. Three main types of affected cells were observed (Figs. 3 to 5). The most common lesion was cells with myofibrils showing various degrees of hypercontraction independent of the noradrenaline concentration in the perfusion solution. The mitochondria were rounded and

**Table 1** Aortic and coronary flow for hearts perfused with different concentrations of noradrenaline (NA) in the perfusion buffer

| (group) | Time (min) | Aortic flow |        |        |         |         | Coronary flow |        |        |        |        |
|---------|------------|-------------|--------|--------|---------|---------|---------------|--------|--------|--------|--------|
|         |            | 0           | 5      | 10     | 15      | 45 + 2  | 0             | 5      | 10     | 15     | 45 + 2 |
| Control |            | 35 ± 2*     | 34 ± 2 | 35 ± 1 | 34 ± 2  | 35 ± 2  | 19 ± 1        | 19 ± 1 | 20 ± 1 | 20 ± 1 | 18 ± 2 |
| NA      |            | 35 ± 1      | 38 ± 2 | 38 ± 1 | 36 ± 2  | 34 ± 3  | 20 ± 1        | 20 ± 0 | 20 ± 1 | 20 ± 1 | 23 ± 2 |
| 10 M    |            |             |        |        |         |         |               |        |        |        |        |
| NA      |            | 37 ± 2      | 35 ± 1 | 36 ± 1 | 36 ± 2  | 29 ± 2† | 20 ± 0        | 20 ± 0 | 21 ± 1 | 21 ± 0 | 20 ± 0 |
| 10 M    |            |             |        |        |         |         |               |        |        |        |        |
| NA      |            | 37 ± 3      | 31 ± 3 | 33 ± 2 | 33 ± 2  | 25 ± 1† | 20 ± 1        | 19 ± 1 | 18 ± 1 | 19 ± 1 | 20 ± 1 |
| 10 M    |            |             |        |        |         |         |               |        |        |        |        |
| NA      |            | 31 ± 1      | 27 ± 2 | 28 ± 1 | 27 ± 1† | 18 ± 2† | 20 ± 2        | 20 ± 1 | 19 ± 1 | 19 ± 1 | 19 ± 1 |
| 10 M    |            |             |        |        |         |         |               |        |        |        |        |

The values are estimated just before addition of noradrenaline and 5, 10 and 15 minutes later. The hearts were then perfused for 30 minutes in the retrograde way and thereafter for 2 minutes as working preparations before the final estimation (45 + 2). Each value represents the mean ± SE for 6 to 8 hearts.

† = significantly different from the initial value ( $p \leq 0.05$ )

Langendorff for 10 minutes and as a working preparation for 2 minutes to allow for stabilization and washout of blood. Thereafter the drugs were added and the hearts subjected to different concentrations of noradrenaline and metoprolol, verapamil or lidocaine were perfused antegrade for 15 minutes and retrogradely for 30 minutes. Hearts exposed to tyramine were perfused antegrade for 60 minutes. The hearts taken for histological examination were perfused antegrade and retrogradely for 60 minutes respectively.

Noradrenaline bitartrate was dissolved in Krebs-Henseleit buffer with ascorbic acid added. One ml of the noradrenaline solution was added to the recirculating buffer to give a final concentration of  $10^{-6}$  M.  $10^{-6}$  M Tyramine HCl was dissolved in the perfusate and added to the recirculating buffer to give a final concentration of 250 µg/ml. Metoprolol\* was dissolved in perfusate to give a final concentration of  $10^{-6}$  M in the buffer used for perfusion of the tyramine-treated hearts and  $10^{-6}$  M for the perfusion of noradrenaline-treated hearts. Standard solutions of lidocaine† and verapamil‡ were used to give final concentrations of  $10^{-6}$  M and  $10^{-6}$  M respectively. Metoprolol, verapamil or lidocaine were added 60 seconds before addition of noradrenaline.

**Chemical analyses** For one group of hearts the

perfusion was terminated by clamping the still beating heart with a Wollenberger clamp precooled in liquid nitrogen. The hearts were powdered in a percussion mortar at the temperature of liquid nitrogen. A sample of this powder was taken for biochemical analysis. Myocardial glycogen was split by amylase and determined according to a glucose oxidase method described by Sifer and Gerstenfeld<sup>14</sup> with rabbit liver glycogen used as a standard. Tissue lactic acid was estimated by the enzymatic method of Lundholm and co-workers.<sup>15</sup> ATP and creatine phosphate contents were assayed by an enzymatic method described by Lamprecht and Traut-schold.<sup>16</sup>

Samples from the perfusion fluid were taken at regular intervals for biochemical analysis. The release of aspartate aminotransferase (ASAT, FC 2611) and creatine phosphokinase (CK, I-C 2732) from the myocardium to the perfusate was estimated by measuring the activities of these enzymes at 35°C in buffer samples using a LKB 8600 Reaction Rate Analyzer\* and standard UV test kits†. The cardiac output and coronary flow were measured by collecting the perfusate in a graduated cylinder and calculating the volume per unit time.

**Histological examinations** The hearts used for histological examination were arrested in diastole by perfusion with buffer at +4°C immediately

\*Metoprolol (Seloken) A. B. Hänsle Göteborg, Sweden.  
†Lidocaine (Xylocard) A. B. Hänsle Göteborg, Sweden.  
‡Verapamil (Isoptin) Knoll A. C. Ludwigshafen am Rhein West Germany.

LKB Bromma Sweden.  
†Biochemical Test Combination Boehringer Mannheim GmbH West Germany.

followed by perfusion with buffer containing glutaraldehyde (2.5 per cent) for 15 minutes at  $+4^{\circ}\text{C}$ . The hearts were then fixed in the glutaraldehyde solution for an additional 6 hours. After fixation the hearts were rinsed in Tyrode's solution while slices of about 1 mm were cut from the midregion of the ventricles. From these slices the free left ventricular wall was subdivided into five groups of tissue blocks of 1 mm<sup>3</sup> so that each group of blocks represented successive layers of the myocardium from the endocardium to the epicardium. The blocks were postfixed in 1 per cent osmium tetroxide in Tyrode's solution for 2 hours, rinsed in buffer, dehydrated in graded series of acetone and finally embedded in Vestopal W. Ultrathin slices were cut in a LKB Ultratome and the slices were collected on formvar coated keyhole or meshgrid stained with uranyl acetate and lead citrate before examination in a Philips EM 300 Electron Microscope.

### Statistics

Comparisons between means were performed with the Student's *t* test. A *p* value  $\leq 0.05$  was considered significant in this study.

### Results

#### Effects of endogenous noradrenaline

**Coronary and aortic flows.** There was no change in coronary flow caused by the addition of noradrenaline to the perfusion medium in concentrations of 10<sup>-7</sup> M to 10<sup>-4</sup> M (Table I). On the other hand there was a decrease in aortic flow at concentrations of 10<sup>-6</sup> M or greater.

**Myocardial content of ATP and creatine phosphate.** Hearts perfused for 45 minutes with noradrenaline had lower contents of ATP but an accumulation of creatine phosphate with increasing noradrenaline concentrations in the buffer (Fig. 1).

**Release of ASAT and CK to the perfusion medium.** There was a leakage of ASAT and CK from well perfused hearts when noradrenaline was added to the perfusion buffer (Fig. 2). A dose-response relationship between the concentration of noradrenaline and the leakage of enzymes was demonstrated. A concentration of 10<sup>-6</sup> M of noradrenaline did not cause a greater leakage of ASAT or CK than in controls. At a concentration

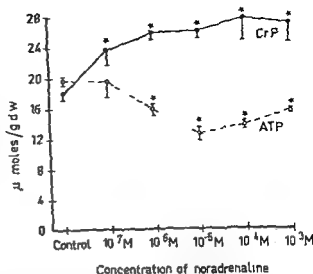


Fig. 1 Effects of different concentrations of noradrenaline on myocardial ATP and creatine phosphate (CrP). The hearts were perfused anterogradely for 15 minutes and retrogradely for 30 minutes. Each value represents the mean  $\pm$  SE for 6 to 8 hearts. \* = significantly different from the control ( $p < 0.05$ ).

of 10<sup>-6</sup> M of noradrenaline however there was a significant leakage of both enzymes which was further increased by 10<sup>-5</sup> M of noradrenaline. Addition of 10<sup>-6</sup> M however did not cause any further increase in leakage. The increases in the activities of ASAT and CK became statistically significant after 25 minutes of perfusion when perfused with noradrenaline 10<sup>-6</sup> M to 10<sup>-5</sup> M.

**Changes in myocardial ultrastructure.** Ultrastructural lesions were seen in the myocardium of hearts perfused with noradrenaline. Damaged muscle fibers were scattered throughout the myocardium without any preferential location. At low concentrations of noradrenaline (10<sup>-7</sup> M) the myocardial lesions consisted mainly of single affected myocardial fibers surrounded by perfectly normal cells. At higher concentrations of noradrenaline the number of damaged cells was increased and clusters of affected cells were seen. The capillaries always appeared to be open and had a normal ultrastructure (Fig. 3). The morphology of the affected cells was highly variable however with regard to the characteristics of the lesions. Three main types of affected cells were observed (Figs. 3 to 5). The most common lesion was cells with myofibrils showing various degrees of hypercontraction independent of the noradrenaline concentration in the perfusion solution. The mitochondria were rounded and

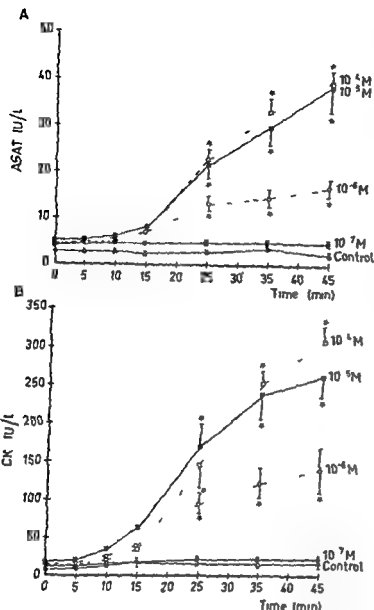


Fig 2 A (upper panel) Release of ASAT from the hearts to the perfusion medium when perfused with different concentrations of noradrenaline. After 15 minutes of antegrade perfusion 30 minutes of retrograde perfusion followed B (lower panel) Release of CK under the same conditions as in panel A. Each value represents the mean  $\pm$  SE for 6 to 8 hearts. \* = significantly different from the initial value ( $p < 0.05$ )

enlarged with an electron translucent matrix often containing flocculent densities and paracrystalline material (Figs 4 and 5). Some of the cells with this type of damage showed signs of disintegration in connection with sarcolemmal ruptures.

The affected myocardial cells of the second type of lesion also contained abnormal myofibrils. The sarcomeric bands were indistinct and especially the A bands were of low density. The mitochondria on the other hand were very electron-dense with inner membranes either in twisted zigzag or tubular configuration (Fig 6).



Fig 3 Low power electron micrograph of cross sectioned myocardium from a rat heart perfused with noradrenaline. 10<sup>-6</sup> M. Normal cells (left part of panel) have a typical pattern of mitochondria and myofibrils. In the affected cells (right part of panel) this regular pattern is lost. A few cells have a high electron opacity (arrows). The distribution of patent capillaries is uniform. (Original magnification  $\times 660$ )

The third type of myocardial cell damage was characterized by cells of a high over all electron opacity. In low magnification in cross sections the normal checkerboard pattern due to myofibrils and mitochondria appeared to be lost (Fig 3). At higher magnification myofibrils with a normal banding pattern could be distinguished interspersed with mitochondria as in normal myocardial fibers.

**Protective effects of metoprolol verapamil and lidocaine on hearts perfused with noradrenaline.** As shown in Fig 2A there was a significant release of ASAT when hearts were perfused with noradrenaline compared to controls. This leakage was significantly reduced by pretreatment with metoprolol verapamil, or lidocaine. There were no significant differences in the release of ASAT between the three groups at the chosen concentrations (Fig 7). The noradrenaline dependent decrease in myocardial ATP content was prevented by metoprolol verapamil or lidocaine. The noradrenaline induced increase of creatine phosphate however did not seem to be prevented by metoprolol verapamil or lidocaine (Table II).

**Effects of tyramine on myocardial contents of ATP, creatine phosphate and leakage of CK.** Tyramine caused no significant reduction in myocardial ATP content (Table III). The increase in creatine phosphate was however not influenced by pretreatment with metoprolol.



Fig 4 Longitudinally sectioned myocardial fibers. The three central fibers contain myofibrils in various stages of hypercontraction. Some extensive contraction bands are indicated by arrows. The mitochondria in these cells are translucent enlarged and often containing matrix densities. The neighbouring cells ( ) contain electron dense mitochondria (m). The myofibrils in these cells have an ill defined banding pattern as described for the second type of lesion in the hearts perfused with noradrenaline. A normal muscle fiber is seen in the upper right corner. = = capillary (Original magnification  $\times 3000$ )

Tyramine perfusion also resulted in a leakage of CK which was significantly reduced during perfusion with tyramine in combination with metoprolol (Fig 8)

### Discussion

The cardiotoxic effects of adrenaline were discovered by Josué already in 1907. Other catecholamines have also been shown to have cardiotoxic effects when given in large doses to animals.<sup>1</sup> High levels of circulating catecholamines in patients with pheochromocytoma are believed to be responsible for the cardiomyopathy seen in this disease. Different mechanisms for the cardiotoxic effect of catecholamines have been suggested including an imbalance between myocardial oxygen demand and supply, platelet

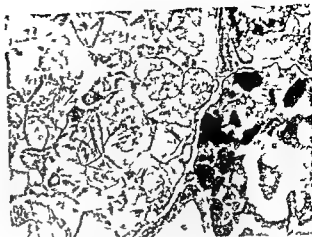


Fig 5 Cross-section of two muscle fibers. The fiber to the left appears relatively normal while the other one shows swollen mitochondria (m) with a translucent matrix. Matrix densities are evident at arrows. = = capillary (Original magnification  $\times 19000$ )

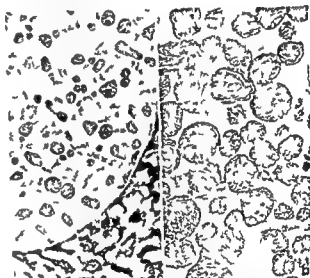


Fig 6 a Cross-section of a myocardial fiber with intracellular edema. Myofibrils appear to be in a stage of lysis (arrows). The mitochondria are dense with inner membranes in a tubular configuration. The adjacent cell is normal in appearance (Original magnification  $\times 3000$ ). b Higher magnification of mitochondria with inner membranes in a tubular or zigzag configuration (Original magnification  $\times 19000$ )

aggregation resulting in coronary thrombus formation<sup>2</sup> and disturbances in microcirculation.

Hearts perfused with noradrenaline were damaged as demonstrated by decreased cardiac output, leakage of myocardial enzymes and ultrastructural alterations. Since an isolated heart preparation perfused with a medium free of



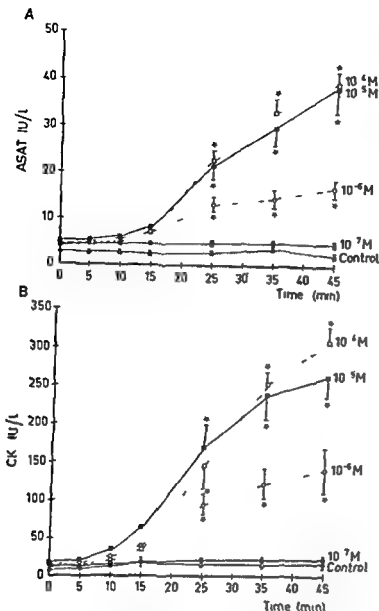


Fig 2 A (upper panel) Release of ASAT from the hearts to the perfusion medium when perfused with different concentrations of noradrenaline. After 15 minutes of antegrade perfusion 30 minutes of retrograde perfusion followed B (lower panel) Release of CK under the same conditions as in panel A. Each value represents the mean  $\pm$  SE for 6 to 8 hearts. \* = significantly different from the initial value ( $p < 0.05$ )

enlarged with an electron translucent matrix often containing flocculent densities and para crystalline material (Figs 4 and 5). Some of the cells with this type of damage showed signs of disintegration in connection with sarcolemmal ruptures.

The affected myocardial cells of the second type of lesion also contained abnormal myofibrils. The sarcomeric bands were indistinct and especially the A bands were of low density. The mitochondria on the other hand were very electron-dense with inner membranes either in twisted zigzag or tubular configuration (Fig 6).



Fig 3 Low power electron micrograph of cross sectioned myocardium from a rat heart perfused with noradrenaline 10<sup>-4</sup>M. Normal cells (left part of panel) have a typical pattern of mitochondria and myofibrils. In the affected cells (right part of panel) this regular pattern is lost. A few cells have a high electron opacity (arrows). The distribution of patent capillaries is uniform. (Original magnification  $\times 600$ )

The third type of myocardial cell damage was characterized by cells of a high over all electron opacity. In low magnification in cross sections the normal checkerboard pattern due to myofibrils and mitochondria appeared to be lost (Fig 3). At higher magnification, myofibrils with a normal banding pattern could be distinguished interspersed with mitochondria as in normal myocardial fibers.

**Protective effects of metoprolol, verapamil and lidocaine on hearts perfused with noradrenaline.** As shown in Fig 2A there was a significant release of ASAT when hearts were perfused with noradrenaline compared to control. This leakage was significantly reduced by pretreatment with metoprolol, verapamil or lidocaine. There were no significant differences in the release of ASAT between the three groups at the chosen concentrations (Fig 7). The noradrenaline-dependent decrease in myocardial ATP content was prevented by metoprolol, verapamil or lidocaine. The noradrenaline induced increase of creatine phosphate however did not seem to be prevented by metoprolol, verapamil or lidocaine (Table II).

**Effects of tyramine on myocardial contents of ATP, creatine phosphate and leakage of CK.** Tyramine caused no significant reduction in myocardial ATP content (Table III). The increase in creatine phosphate was however not influenced by pretreatment with metoprolol.

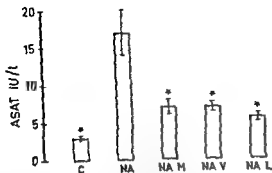


Fig 7 Release of ASAT from hearts perfused anterogradely for 15 minutes and retrogradely for 30 minutes with noradrenaline 10  $\mu$ M (NA) and metoprolol 10  $\mu$ M (M) verapamil 10  $\mu$ M (V) or lidocaine 10  $\mu$ M (L). Each bar represents the mean  $\pm$ SE for 6 to 8 hearts. \* = significantly different from NA ( $p < 0.05$ ).

tion. A membrane stabilizing effect of this drug has also been proposed. Local application of lidocaine on experimental ischemic dog hearts has been shown to decrease noradrenaline release though the mechanism of this effect is not fully understood.<sup>2</sup>

Ultrastructural examination of the hearts also revealed the dose dependent damage caused by noradrenaline. However it was evident that different types of lesions of myocardial cells were inflicted by noradrenaline perfusion. At least three types of myocardial fiber lesions were observed. The most frequent type of lesion—myocardial fibers with hypercontracted myofibrils and swollen mitochondria—has previously been recognized by many investigators as characteristic of many cardiomyopathies especially those related to catecholamine induced necrosis.<sup>3</sup> This type of lesion was referred to as coagulative myocytolysis by Baroldi,<sup>1</sup> who observed it in 68 per cent of patients with sudden coronary deaths.

The second type of lesion in this study consisted of myocardial cells with myofibrils in a stage of lysis and mitochondria that *in situ* according to the terminology of Korman and co-workers,<sup>10</sup> can be referred to as having an energized twisted or zigzag configuration. Whether the structure of such mitochondria does reflect different metabolic states or not has been debated extensively. The proposal that the intramitochondrial reorganization represents a mechanism for energy conservation has been discarded. It seems more likely that such changes are involved

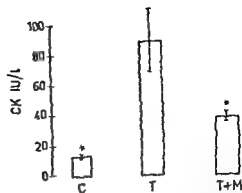


Fig 8 Release of CK from hearts perfused anterogradely for 60 minutes with tyramine 250  $\mu$ g/ml (T) with or without metoprolol 10  $\mu$ M (M). Controls are perfused without addition of tyramine or metoprolol. Each bar represents the mean  $\pm$ SE for 6 to 8 hearts. \* = significantly different from tyramine treated hearts ( $p < 0.05$ ).

in metabolic control.<sup>9</sup> Undoubtedly the metabolic situation in this type of lesion is different from that in the previous type. This second type of lesion might correspond to the lesion which Baroldi<sup>10</sup> called colliquative myocytolysis and which is supposed to be typical of cells dying in a failing state.

The third type of lesion seen here might be the same as that of certain cells seen in human myocardial lesions in which the structure of the entire cell is indistinct.<sup>3</sup>

It can be concluded that the diversity of reactions in the myocardial cells appears to be independent of the relationship between cells and capillaries since the lesions are diffusely scattered over the myocardium and the capillaries were uniformly patent.

The biochemical analyses of whole hearts do of course reflect the combined effects of all the cells. Since the far most common lesion was of the first type i.e. the type found in cardiomyopathy enzyme release is probably related to this type of lesion. The unpredictable rise of creatine phosphate might on the other hand be related to other types of lesions. The ultrastructure of noradrenaline perfused hearts was similar to that seen in ischemia<sup>4</sup> and may be related to the different types of lesions described by Baroldi.<sup>3</sup> Thus catecholamines may induce myocardial cell damage of the same type as seen in acute myocardial infarction.

The initial event leading to acute myocardial infarction has recently been debated.<sup>1</sup> The present study has shown the detrimental effects

**Table II** Effects on myocardial ATP and creatine phosphate for hearts perfused with noradrenaline  $10^{-6}$  M and in presence of metoprolol  $10^{-6}$  M verapamil  $10^{-6}$  M or lidocaine,  $10^{-6}$  M

|  | Control       | NA†            | NA + M         | NA + V         | NA + L        |
|--|---------------|----------------|----------------|----------------|---------------|
| ATP ( $\mu\text{mol/Gm dry weight}$ )                | $197 \pm 0.6$ | $159 \pm 0.6†$ | $213 \pm 2.3$  | $205 \pm 0.8$  | $219 \pm 1.4$ |
| Creatine phosphate ( $\mu\text{mol/Gm dry weight}$ ) | $183 \pm 1.0$ | $258 \pm 1.3†$ | $283 \pm 2.1†$ | $306 \pm 1.6†$ | $286 \pm 1.5$ |

The hearts were perfused for 15 minutes as working preparations and retrogradely for 30 minutes. Each value represents the mean  $\pm$  SE for 5 to 6 hearts.

† = significantly different from controls ( $p \leq 0.05$ ).

Abbreviations: NA = noradrenaline, M = metoprolol, V = verapamil, L = lidocaine.

**Table III** Effects on myocardial ATP and creatine phosphate for hearts perfused with tyramine  $250 \mu\text{g/ml}$ , with or without metoprolol  $10^{-6}$  M

|  | Control         | Tyramine      | Tyramine + metoprolol |
|--|-----------------|---------------|-----------------------|
| ATP ( $\mu\text{mol/Gm dry weight}$ )                | $161 \pm 0.5^*$ | $153 \pm 0.6$ | $173 \pm 1.0$         |
| Creatine phosphate ( $\mu\text{mol/Gm dry weight}$ ) | $223 \pm 1.4$   | $245 \pm 0.6$ | $260 \pm 1.7$         |

The hearts were perfused for 60 minutes as working preparations. Each value represents the mean  $\pm$  SE for 5 to 6 hearts.

blood was used the demonstrated effects of noradrenaline could not have been due to effects of the sympathetic nervous system lysis of adipose tissue or reduction of coronary flow due to platelet aggregation. The dose dependent effects of noradrenaline on the leakage of ASAT and CK speak in favor of the theory of increased metabolic demand as the cause of the myocardial damage seen in this study.

The normal plasma adrenaline level under physiological conditions is in the order of  $10^{-6}$  M to  $10^{-7}$  M. The noradrenaline concentration of rat myocardium is about  $600 \text{ ng/Gm}$ . The concentration of noradrenaline in a homogenate of heart can thus be expected to be about  $10^{-6}$  M. The higher concentrations of noradrenaline used in this study were unphysiological but local concentrations of noradrenaline within the heart can be in the order of  $10^{-6}$  M or even higher if the myocardial stores of noradrenaline are rapidly depleted during anoxia or ischemia as shown by Wollenberger and associates.<sup>2</sup>

The sympathomimetic action of tyramine is exclusively due to the depletion of catecholamine stores. When tyramine was added to the perfusion buffer there was a marked release of CK which was prevented by concomitant perfusion

with the beta blocker metoprolol. This indicated that the amount of noradrenaline stored in the heart is enough to induce cellular damage. Since leakage of CK and decrease of ATP are prevented by metoprolol it seems that the adverse effects of tyramine are mediated via beta receptors and are not unspecific toxic effects.

Noradrenaline did not alter coronary flow but with noradrenaline concentrations of  $10^{-6}$  M or more there was a reduction of cardiac output as a sign of cardiac failure and leakage of CK indicating cell damage. As already shown by others,<sup>1</sup> myocardial glycogen was depressed and lactate accumulated in catecholamine perfused hearts. The decrease of ATP content has been described earlier<sup>1</sup> but the concomitant increase of creatine phosphate content found here needs further explanation. When isoproterenol was given to rats a decrease of myocardial ATP was demonstrated while creatine phosphate levels were still unchanged.<sup>1</sup> One explanation might be a decreased activity of the pH sensitive CK due to lactate accumulation. The release of CK from the heart demonstrated in this study will further reduce the intracellular activity of this enzyme.

The effects on the slow  $\text{Ca}^{2+}$  channels of the cell membrane by catecholamines<sup>3</sup> result in enhanced  $\text{Ca}^{2+}$  influx which in turn may cause  $\text{Ca}^{2+}$  overload and cellular injury as proposed by Fleckenstein and co-workers.<sup>4</sup> The cardioselective beta blocker metoprolol and the membrane stabilizing agent lidocaine as well as the calcium antagonistic drug verapamil all showed protective effects against noradrenaline induced myocardial damage by their respective specific actions at different cellular levels. Beneficial effects of beta blockade on the ischemic myocardium have been described earlier.<sup>5</sup> Similar effects on ischemic myocardium by verapamil<sup>6</sup> are probably due to the  $\text{Ca}^{2+}$  antagonistic effect resulting in decreased myocardial work and oxygen consumption.

- 21 Snider S R Almgren O and Carlsson A The occurrence and functional significance of dopamine in some peripheral adrenergic nerves of the rat *Naunyn-Schmiedeberg's Arch Pharmacol* 278 1 1973
- 22 Wollenberger A and Shahab L Anoxia induced release of noradrenaline from the isolated perfused heart *Nature* 207 68 1965
- 23 Weiner N Dra koczy P R and Burack W R The ability of tyramine to liberate catecholamines *in vivo* *J Pharmacol. Exp Ther* 137 47 1962
- 24 Williamson J R Metabolic effects of epinephrine in the perfused rat heart II Control steps of glucose and glycogen metabolism *Mol. Pharmacol* 2 206 1966
- 25 Williamson J R Metabolic effects of epinephrine in the isolated perfused rat heart I Dissociation of the glycolytic from the metabolic stimulatory effect *J Biol Chem* 239 2791 1964
- 26 Takenaka F and Higuchi M High-energy phosphate contents of subepicardium and subendocardium in the rat treated with isoproterenol and some other drugs *J Mol Cell Cardiol* 11 123 1974
- 27 Sperelakis N and Schneider J A A metabolic control mechanism for calcium ion influx that may protect the ventricular myocardial cell *Am J Cardiol* 37 10 9 1976
- 28 Fleckenstein A Janke J Dongg H J and Pachinger O Ca overload as the determinant factor in the production of catecholamine induced myocardial lesions in Recent advances in studies on cardiac structure and metabolism vol 2 *Cardiomyopathies* eds E Bajusz and W Rona Munten/Berlin Wien 1974 Urban & Schwarzenberg p 450
- 29 Maroko P R Libby I and Braunwald E Effect of pharmacologic agents on the function of the ischemic heart *Am J Cardiol* 32 930 1973
- 30 Mueller H Propranolol in acute myocardial infarction in man Effects of hemodynamics and myocardial oxygenation *Acta Med Scand (suppl)* 587 177 1975
- 31 Waagstein F and Hjalmarson A C Effect of cardio selective beta blockade on heart function and chest pain in acute myocardial infarction *Acta Med Scand (suppl)* 587 193 1975
- 32 Fleckenstein A Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention or production of myocardial lesions in *Calcium and the heart* eds P Harris and L H Opie London 1971 Academic Press p 135
- 33 Staszewska Barczak J The reflex stimulation of catecholamine secretion during the acute stage of myocardial infarction in the dog *Clin Sci* 41 419 1971
- 34 Reschenbach D and Benditt E Catecholamines and cardiomyopathy The pathogenesis and potential importance of myofibrillar degeneration *Human Pathol* 1 120 1970
- 35 Baroldi C Myocardial necrosis The need for definition *J Mol Cell Cardiol* 6 401 1974
- 36 Korman E F Addink D F Walabayashi T and Green D E A unified model of mitochondrial morphology *J Bioenergetics* 1 9 1971
- 37 Ferrans V J Hibbs R G Weihs H S Weibsaecher D G Walsh J J and Burch G E A histochemical and electron microscopic study of epinephrine induced myocardial necrosis *J Mol Cell Cardiol* 1 11 1970
- 38 Moravcsik J Corsin J, Guillemot H and Hatt F J Absence of relationship between ultrastructure and metabolic state of heart mitochondria *in situ* *J Mol Cell Cardiol* 2 161 1971
- 39 Munn E A Relationships between mitochondrial structure metabolic control and ion transport in *The Structure of mitochondria* London and New York 1974 Academic Press p 30
- 40 Jennings R B Relationship of acute ischemia to functional defects and irreversibility *Circulation* 53 1 1976
- 41 Wilhelmsson C Uden J A Wilhelmsson L Tibblin C and Werkö L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol *Lancet* 2 115 1974

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material."

of exogenous noradrenaline on well perfused hearts. The fact that the rapid release of myocardial stores of noradrenaline can result also in ischemic damage to well perfused hearts supports the theory of an imbalance between the myocardial metabolic demand and the supply of oxygen, fluids and substrates. It is also well known that short periods of anoxia and ischemia cause a release of myocardial noradrenaline which may well lead to an aggravation of the primary ischemia.

From this study it can be hypothesized that acute myocardial infarction may start with a temporary relative ischemia due to a sudden increase of metabolic demand and/or atherosclerotic narrowing of coronary vessels. This results in a release of stored noradrenaline that starts a vicious cycle with a further increase of the ischemic damage. The protective effects of beta blockade on the ischemic myocardium<sup>2,3</sup> as well as the possible preventive effects in patients who sustained acute myocardial infarction<sup>4</sup> might at least partly be explained by the proposed role of noradrenaline in myocardial infarction.

### Summary

Isolated rat hearts were perfused with buffer containing noradrenaline  $10^{-7}$  to  $10^{-6}$  M. A dose dependent depletion of glycogen and ATP were seen together with a leakage of ASAT and creatine phosphokinase (CK). The damage induced by noradrenaline could be prevented by addition of a beta blocker (metoprolol), verapamil or lidocaine to the perfusion medium. When the endogenous myocardial stores of noradrenaline are rapidly depleted by perfusion with tyramine a similar cell damage was demonstrated. Electron micrographs from hearts subjected to noradrenaline showed three different types of cell damage that could be correlated to earlier described findings. The importance of noradrenaline for the ischemic injury was demonstrated. It was hypothesized that acute myocardial infarction may start because of a sudden release of endogenous noradrenaline.

### REFERENCES

- Chapman I. Relationships of recent coronary artery occlusion and acute myocardial infarction. *J Mt Sinai Hosp* 35:149, 1968.
- Schwartz C J and Mitchell J R A. The relation between myocardial lesions and coronary artery disease. I. An unselected necropsy study. *Br Heart J* 24:711, 1962.
- Sinapius D. Beziehungen zwischen Koronar thrombose und Myokard infarkten. *Dtsch Med Wochenschr* 97:443, 1972.
- Roberts W C and Buys L M. The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction. A study of 107 necropsy patients. *Am J Med* 52:425, 1972.
- Baroldi G. Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death. *Am J Cardiol* 16:839, 1965.
- Friedrich L R, Lundman T and Mellstedt H. Incorporation of <sup>125</sup>I labelled fibrinogen into coronary arterial thrombi in acute myocardial infarction in man. *Lancet* 1:387, 1973.
- Shahab L, Wollenberger A, Haase M and Schliker U. Noradrenalinabgabe aus dem Hundeherzen nach vorübergehender Okklusion einer Koronararterie. *Acta Biol Med Germ* 22:133, 1969.
- Szaszewska-Barczak J and Czeremuzynski L. The continuous estimation of catecholamine release in the early stages of myocardial infarction in the dog. *Clin Sci* 34:531, 1968.
- Neely J R, Liebermeister H, Batterby F J and Morgan H P. Effect of pressure development on oxygen consumption by isolated rat heart. *Am J Physiol* 212:894, 1967.
- Waldenström A P and Hjalmarson A C. Myocardial enzyme release from ischemic isolated perfused working rat heart. In: Recent advances in studies on cardiac structure and metabolism, vol. 10. The metabolism of contraction, eds P F Rov and C Rona. Baltimore, 1975. University Park Press, p. 307.
- Safer A and Cerstenfeld S. The photometric microdetermination of blood glucose with glucose oxidase. *J Lab Clin Med* 51:488, 1958.
- Lundholm L, Mohme Lundholm F and Vamoss A. Lactic acid assay with (+) lactic acid dehydrogenase from rabbit muscle. *Acta Physiol Scand* 88:243, 1971.
- Lamprecht W and Trautwein J. Determination with hexokinase and glucose 6 phosphate dehydrogenase. In: Methods of enzymatic analysis. Adenine 5 triphosphate ed H U Bergmeyer. New York and London 1963. Academic Press Verlag Chemie GmbH Weinheim, p. 543.
- José O. Hypertrophie cardiaque causée par l'adrénaline et la toxine typhique. *C R Soc Biol (Paris)* 63:190, 1907.
- Rona C, Chappel C I, Bilitz T and Gaudry R. An infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat. *Arch Pathol* 67:443, 1969.
- van Vleet P D, Burchell H H and Titus J L. Focal myocarditis associated with pheochromocytoma. *N Engl J Med* 274:1102, 1966.
- Rash W, van Lath P, Lapreschkin F and Herrlich H C. Catecholamine induced myocardial hypoxia in the presence of impaired coronary distal flow independent of external cardiac work. *Am J Cardiol* 9:4, 1962.
- Hill J I and Fain R. Stress and the induction of intravascular platelet aggregation in the heart. *Circulation* 48:164, 1973.
- Boutet M, Huttner L and Rona C. Effect of isoproterenol on the coronary microcirculation. Studies with protein tracers (Abstract). *Lab Invest* 26:471, 1971.
- Hickler H H, Wells R E, Tyler H R and Hamlin J T. Plasma catecholamines and electrocardiographic responses to acute postural change. Evidence of a deficient pressor amine response in postural hypertension. *Am J Med* 26:410, 1959.

- 21 Snider R, Almgren O and Carlsson A. The occurrence and functional significance of dopamine in some peripheral adrenergic nerves of the rat. *Naunyn-Schmiedeberg Arch Pharmacol* 278:1 1973
- 22 Wollenberger A and Shahab L. Anoxia induced release of noradrenaline from the isolated perfused heart. *Nature* 207:58 1965
- 23 Weiner N, Draskoczy P R and Butack W R. The ability of tyramine to liberate catecholamines *in vivo*. *J Pharmacol Exp Ther* 137:47 1967
- 24 Williamson J R. Metabolic effects of epinephrine in the perfused rat heart II. Control steps of glucose and glycogen metabolism. *Mol Pharmacol* 2:206 1966
- 25 Williamson J R. Metabolic effects of epinephrine in the isolated perfused rat heart I. Dissociation of the glycolytic from the metabolic stimulatory effect. *J Biol Chem* 239:721 1964
- 26 Takenaka F and Higuchi M. High-energy phosphate contents of subepicardium and subendocardium in the rat treated with isoproterenol and some other drugs. *J Mol Cell Cardiol* 6:123 1974
- 27 Sperelakis N and Schneider J A. A metabolic control mechanism for calcium ion influx that may protect the ventricular myocardial cell. *Am J Cardiol* 37:1079 1976
- 28 Fleckenstein A, Janke J, Döring H J and Pachinger O. Ca overload as the determinant factor in the production of catecholamine induced myocardial lesions in Recent advances in studies on cardiac structure and metabolism vol 9. *Cardiomyopathies* eds E Bajusz and C Rona. München/Berlin/Wien 1974 Urban & Schwarzenberg p 435
- 29 Maroko P R, Libby P and Braunwald E. Effect of pharmacologic agents on the function of the ischemic heart. *Am J Cardiol* 32:930 1973
- 30 Mueller H. Propranolol in acute myocardial infarction in man. Effects of hemodynamics and myocardial oxygenation. *Acta Med Scand (suppl)* 587:17 1975
- 31 Wasgstein F and Hjalmarsson Å C. Effect of cardio selective beta blockade on heart function and chest pain in acute myocardial infarction. *Acta Med Scand (suppl)* 587:193 1975
- 32 Fleckenstein A. Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention or production of myocardial lesions in Calcium and the heart eds P Harris and L H Opie. London 1971 Academic Press p 133
- 33 Staszewska Barczak J. The reflex stimulation of catecholamine secretion during the acute stage of myocardial infarction in the dog. *Clin Sci* 41:419 1971
- 34 Reichenbach D and Benditt E. Catecholamines and cardiomyopathy. The pathogenesis and potential importance of myofibrillar degeneration. *Human Pathol* 1:12 1970
- 35 Baroldi G. Myocardial necrosis. The need for definition. *J Mol Cell Cardiol* 11:401 1974
- 36 Korman E F, Addink D F, Wakabayashi T and Green D E. A unified model of mitochondrial morphology. *J Bioenergetics* 1:9 1970
- 37 Ferrans V J, Hibbs R C, Wiley H S, Weilbaecher D G, Walsh J J and Burch G. A histochemical and electron microscopic study of epinephrine induced myocardial necrosis. *J Mol Cell Cardiol* 1:11 1970
- 38 Moravec J, Corsin J, Guillemot H and Hatt P J. Absence of relationship between ultrastructure and metabolic state of heart mitochondria *in situ*. *J Mol Cell Cardiol* 2:161 1971
- 39 Munn E A. Relationships between mitochondrial structure, metabolic control and ion transport in the structure of mitochondria. London and New York 1974 Academic Press p 370
- 40 Jennings R. Relationship of acute ischemia to functional defects and irreversibility. *Circulation* 53:1 1976
- 41 Wilhelmsson C, Vedin J A, Wilhelmsson L, Tibblin G and Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 2:1157 1974

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author:

The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

# Components of the hemodynamic response to elevated cerebrospinal fluid pressure

Richard E. Brashear, M.D.  
Pro lo Yu, Ph.D.  
Indianapolis, Ind.

Elevation of cerebrospinal fluid (CSF) pressure to levels usually exceeding mean systemic blood pressure is followed by what is frequently called the Cushing reflex.<sup>1</sup> The increased vascular pressures and cardiac output occurring with the reflex have been well described.<sup>2</sup> Since intracranial pressures may increase to over 100 mm Hg with severe brain injury<sup>3</sup> and intracranial pressures up to 160 mm Hg have been described in patients with subarachnoid hemorrhage,<sup>4</sup> significant elevations of intracranial pressure have clinical importance.

We have previously demonstrated that increasing CSF pressure to 200 mm Hg significantly increased cardiac output, heart rate, stroke volume, aortic pressure, pulmonary artery pressure, wedge pressure, right atrial pressure, pulmonary capillary blood volume, and pulmonary diffusing capacity.<sup>5</sup> These changes were attributed to a massive alpha and beta adrenergic stimulation. Beta adrenergic blockade prevented an increase in cardiac output and heart rate but did not alter the response of increased vascular pressures to elevated CSF pressure. Alpha adrenergic blockade prevented an increase in vascular pressures during elevated CSF pressure but did not prevent the increase in cardiac output. Two distinct adrenergic components were thus identified but it was unclear if the components were humoral or neurogenically mediated. A subsequent study provided evidence for a circulating beta adrenergic agonist during elevated CSF pressure.<sup>6</sup> The

present study was undertaken to clarify the origin of these alpha and beta adrenergic effects during elevated cerebrospinal fluid pressure.

## Methods

Mongrel dogs ( $21 \pm 3$  kilograms, mean  $\pm$  SD) were anesthetized with pentobarbital (30 mg/kg) intravenously. Ventilation with periodic hyperventilation was controlled through a cuffed endotracheal tube with a Harvard constant volume ventilator. End tidal  $CO_2$  was monitored and maintained between 50 to 55 per cent and the animals were paralyzed with intravenous gallamine triethiodide (2.0 mg/kg).

For clarification the various subgroups studied with elevated CSF pressure are outlined as follows:

Group I: An initial six dogs studied acutely after bilateral adrenalectomy and ganglionic blockade with hexamethonium.

Group II: Six dogs studied  $17 \pm 2$  days after adrenalectomy.

Group III: Twelve dogs studied with an isolated and perfused gracilis muscle preparation and beta adrenergic blockade.

Group III A: Four studied with intact adrenals with the muscle preparation denervated.

Group III B: Four studied  $18 \pm 1$  days after adrenalectomy with the muscle preparation denervated.

Group III C: Four studied  $18 \pm 2$  days after adrenalectomy with muscle preparation innervated.

Group IV: Six dogs with an isolated perfused and denervated gracilis muscle preparation, alpha adrenergic blockade and intact adrenals.

Groups I and II were studied as previously described.<sup>5,6</sup> Cardiac catheters were placed in the main pulmonary artery, right atrium, and wedge

From the Department of Medicine, Indiana University Medical Center, Indianapolis, Ind.

Received for publication Dec. 8, 1976.

Accepted for publication Feb. 10, 1977.

Reprint request: Richard E. Brashear, M.D., Department of Medicine, Indiana University Medical Center, 1100 West Michigan St., Indianapolis, IN 46202.

position through the jugular veins and in the ascending aorta just distal to the aortic valve through the carotid artery. Pressures were measured at end expiration and heart rate was determined from the pressure tracing. Cardiac outputs were done in duplicate by the indicator-dilution technique and expressed as milliliters per minute per kilogram of body weight and stroke volume as milliliters per beat per kilogram. Central blood volume was determined from the main pulmonary artery to ascending aorta. Mean pressures were used to calculate vascular resistance. Systemic vascular resistance (units) = systemic artery pressure - right atrial pressure (mm Hg)/cardiac output (ml/min per kilogram). Pulmonary vascular resistance (units) = pulmonary artery pressure - wedge pressure (mm Hg)/cardiac output (ml/min per kilogram). Arterial blood pH,  $P_{O_2}$  and  $P_{CO_2}$  were determined by conventional electrodes (Instrumentation Laboratory, Inc.).

Cerebrospinal fluid pressure was elevated as previously described using a pressure reservoir of saline (37°C) buffered with  $NaHCO_3$  to pH 7.4 connected to a needle in the cisterna magna. After control period values were obtained the CSF pressure was increased to 100 mm Hg and measurements were obtained after 5 and 10 minutes. The CSF pressure was then increased to 200 mm Hg, the determinations repeated after 5 and 10 minutes and the CSF pressure was returned to control period levels. The previously mentioned determinations were repeated 10 minutes after CSF pressure was returned to control values.

In Group I the animals were studied immediately after bilateral adrenalectomy and ganglionic blockade obtained with intravenous hexamethonium chloride 5 mg of base per kilogram in a concentration of 25 mg/ml infused over 5 minutes. Completeness of ganglionic blockade was determined by observing mean systemic blood pressure during 30 seconds of bilateral common carotid artery occlusion. Hydrocortisone sodium succinate was given 50 mg intramuscularly at onset of adrenalectomy and 100 mg intravenously during the remainder of the study. Performing the elevated CSF pressure study immediately after adrenalectomy resulted in protracted experiments of 4 to 5 hours.

Subsequently in Groups II and III bilateral adrenalectomy was performed through a midline

incision with sterile technique, meticulous dissection and hemostasis. Dogs were maintained after adrenalectomy with 125 mg cortisone acetate and 1 mg desoxycorticosterone acetate intramuscularly each day. On the day when the dogs were subsequently studied with elevated CSF pressure 14 to 19 days post adrenalectomy they received a 25 mg intravenous bolus of hydrocortisone sodium succinate and an additional 25 mg in 50 ml of saline infused during the remaining study. The amount of steroid was considered to reasonably approximate the amount that would be elaborated during severe stress by an animal with intact adrenals.

The isolated perfused gracilis muscle was prepared in the dog as previously described.<sup>10,11</sup> Briefly the gracilis muscle was completely exposed and isolated except for minimal lateral and medial tendinous connections and the gracilis artery and vein. The obturator nerve was sectioned in the denervated muscle preparations. Heparin 5 mg/kg was given intravenously and a polyethylene catheter (PE 90) was inserted in the gracilis artery and connected to a constant volume flow rate pump (Holter Pump Model 911). The contralateral femoral artery was cannulated for inflow to the pump and flow rate ( $11.5 \pm 2.8$  ml per minute mean  $\pm$  SD) was adjusted so gracilis perfusion pressure approximated systemic blood pressure. Pressure was monitored in the tubing between the femoral artery and perfusion pump permitting the inflow pressure to the pump to be kept constant at control levels regardless of increases in femoral artery pressure by using a screw resistor. After stabilization of the muscle perfusion pressure the propranolol or phenoxvbenzamine were infused.

The 12 dogs (Group III) with beta adrenergic blockade and the isolated perfused gracilis muscle preparation received propranolol 0.5 mg/kg in 30 ml saline over 5 minutes prior to obtaining control values and an additional 0.25 mg/kg in 30 ml over the remainder of the study. Four were studied with intact adrenals and denervated muscle preparation (Group III A). Four were studied after adrenalectomy with denervated muscle preparation (Group III B). Four were studied after adrenalectomy with the muscle preparation innervated (Group III C). At the conclusion of the study the completeness of beta blockade was demonstrated with intravenous isoproterenol (0.01 mg in 20 ml saline over 2



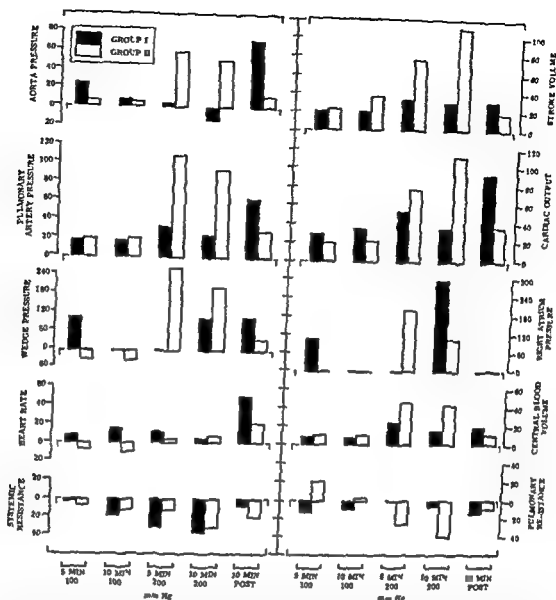


Fig. 1 Per cent change from control during elevated CSF pressure. Group I—adrenalectomy and ganglionic blockade. Group II—adrenalectomy. Abscissa indicates duration and magnitude of elevated CSF pressure. 10 minutes post indicates time after CSF pressure returned to control values. Asterisk indicates change significant at  $P < 0.05$  level.

minutes) demonstrating no change in heart rate, systemic blood pressure, or gracilis muscle resistance.

The six  $\alpha$  adrenergic blockade animals (Group IV) all with intact adrenals and an isolated denervated and perfused gracilis muscle preparation received phenylephrine hydrochloride (courtesy Smith Kline and French Co., Philadelphia) 3 mg/kg in 25 ml saline over 60 minutes prior to obtaining values and an additional 1 mg/kg in 25 ml over the remainder of the study. At the conclusion, the completeness of  $\alpha$  blockade was demonstrated with norepinephrine base 0.01 mg in 20 ml saline intravenously over 2 minutes demonstrating no change in heart rate, systemic blood pressure, or gracilis muscle resistance.

The significance of the change from the control period to each of the subsequent periods was determined by Dunnett's *t* test at the 5 per cent level.<sup>14</sup>

### Results

The results are presented in Figs. 1 and 2. In Group I animals studied acutely after adrenalectomy and ganglionic blockade, control aortic pressure ( $92 \pm 8$  mm Hg, mean  $\pm$  SD) only changed 10 minutes after CSF pressure was returned to control values. Control cardiac output ( $123 \pm 15$  ml/min per kilogram) increased significantly ( $P < 0.05$ ) at 5 minutes of 200 mm Hg CSF pressure and 10 minutes after CSF pressure returned to control levels. Control systemic vascular resistance ( $0.74 \pm 0.07$  units/

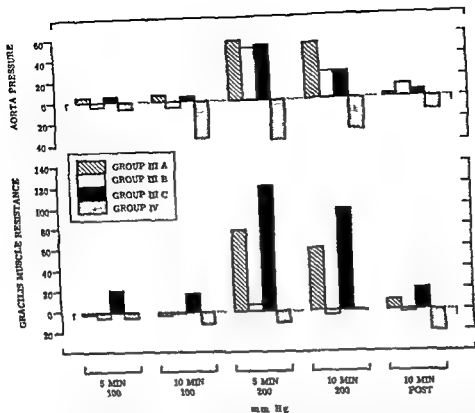


Fig 2 Per cent change from control in gracilis muscle study Group III—beta adrenergic blockade A—intact adrenals denervated muscle B—adrenalectomy denervated muscle C—adrenalectomy innervated muscle Group IV—alpha adrenergic blockade intact adrenals denervated muscle Abscissa and asterisk same as in Fig 1

kilogram) decreased significantly at 10 minutes 100 mm Hg and 5 minutes and 10 minutes of 200 mm Hg CSF pressure. Control right atrial ( $-1 \pm 1$  mm Hg) and wedge ( $1 \pm 3$  mm Hg) pressures showed essentially no change but control pulmonary artery pressure ( $13 \pm 2$  mm Hg) increased slightly but significantly during 5 minutes 200 mm Hg CSF pressure and 10 minutes after release of CSF pressure. Control heart rate ( $111 \pm 8$  beats/minute) increased significantly 10 minutes after release of CSF pressure.

There were no significant changes compared to the control period for any parameter after 5 or 10 minutes of CSF pressure 100 mm Hg in Group II. In Group II control aortic pressure ( $126 \pm 11$  mm Hg), pulmonary artery pressure ( $11 \pm 3$  mm Hg), wedge pressure ( $3 \pm 4$  mm Hg), cardiac output ( $177 \pm 41$  ml/min per kilogram), stroke volume ( $0.99 \pm 0.17$  ml/beat per kilogram) and central blood volume ( $152 \pm 22$  ml/kg) increased significantly ( $P < 0.05$ ) at 5 and 10 minutes of CSF pressure 200 mm Hg. Group II also demon-

strated a significant decrease from control systemic vascular resistance ( $0.758 \pm 0.183$  units/Kg) at 10 minutes of 200 mm Hg and after release of CSF pressure. Group II demonstrated no significant changes in pulmonary vascular resistance or heart rate while a change in right atrial pressure was significant but small.

In Group II the animals were weighed daily after the adrenalectomy and the weight decreased  $1 \pm 1$  kilogram prior to the elevated CSF pressure study. Serum electrolytes were determined on the day of the CSF study and were sodium  $144 \pm 1$  potassium  $4.4 \pm 0.3$  and chloride  $108 \pm 4$  mEq/L.

There were no changes during CSF pressure 100 mm Hg in the beta adrenergic blockade dogs (Fig 2) with the perfused gracilis muscle preparations (Group III). In the animals with intact adrenals and denervated muscle (Group III A) the control aortic pressure ( $131 \pm 5$  mm Hg) increased significantly during 5 and 10 minutes of CSF pressure 200 mm Hg. The resistance of the perfused gracilis muscle increased significantly

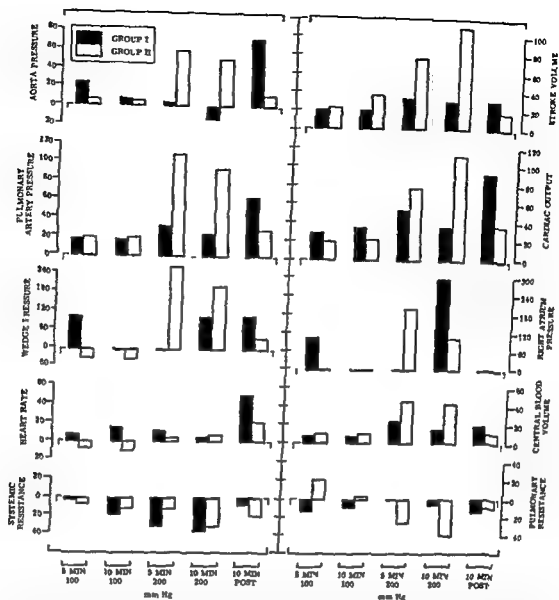


Fig 1 Per cent change from control during elevated CSF pressure. Group I—adrenalectomy and ganglionic blockade. Group II—adrenalectomy. Abscissa indicates duration and magnitude of elevated CSF pressure. 10 minutes post indicates time after CSF pressure returned to control values. Asterisk indicates change significant at  $P < 0.05$  level.

minutes) demonstrating no change in heart rate, systemic blood pressure or gracilis muscle resistance.

The six alpha adrenergic blockade animals (Group IV) all with intact adrenals and an isolated denervated and perfused gracilis muscle preparation received phenoxybenzamine hydrochloride (courtesy Smith Kline and French Co. Philadelphia) 3 mg/kg in 25 ml saline over 60 minutes prior to obtaining values and an additional 1 mg/kg in 25 ml over the remainder of the study. At the conclusion the completeness of alpha blockade was demonstrated with norepinephrine base 0.01 mg in 20 ml saline intravenously over 2 minutes demonstrating no change in heart rate, systemic blood pressure or gracilis muscle resistance.

The significance of the change from the control period to each of the subsequent periods was determined by Dunnett's  $t$  test at the 5 per cent level.<sup>12</sup>

## Results

The results are presented in Figs 1 and 2. In Group I animals studied acutely after adrenalectomy and ganglionic blockade, control aortic pressure ( $92 \pm 8$  mm Hg, mean  $\pm$  SD) only changed 10 minutes after CSF pressure was returned to control values. Control cardiac output ( $123 \pm 15$  ml/min per kilogram) increased significantly ( $P < 0.05$ ) at 5 minutes of 200 mm Hg CSF pressure and 10 minutes after CSF pressure returned to control levels. Control systemic vascular resistance ( $10.7 \pm 0.07$  units/

ade There was no increase in aortic pressure during elevated CSF pressure but cardiac output increased and systemic vascular resistance decreased indicating the presence of a circulating beta adrenergic agonist independent of the adrenals. The previous study also indicated a circulating beta adrenergic agonist but the adrenals were intact.<sup>2</sup> The decrease in control blood pressure was consistent with the lowering of blood pressure found in rats and rabbits with combined chemical sympathectomy and adrenalectomy. A marked increase in cardiac output and aortic pressure occurred 10 minutes after CSF pressure was returned to control levels; this was noted previously in dogs with systemic hypotension during the increased CSF pressure. Dogs can survive 25 minutes of cerebral ischemia<sup>22</sup> and a marked reactive hyperemia occurs with reperfusion of the brain<sup>2</sup> that may wash out vasoactive substances.<sup>2</sup>

Group II (adrenalectomized animals) demonstrated the expected alpha and beta adrenergic effects (increase in vascular pressure, cardiac output, stroke volume) during CSF pressure of 200 mm Hg and therefore excluded the adrenals as the only participant in the Cushing reflex. Other investigators have noted that adrenalectomy in rats does not blunt the rise in blood pressure evoked by brainstem lesions.<sup>2</sup>

Group I (acute adrenalectomy and ganglionic blockade) demonstrated the beta adrenergic effect of increased cardiac output and decreased systemic resistance but essentially no alpha adrenergic effect. This implies the alpha adrenergic effect is lacking because of neurogenic blockade or absent adrenal secretions. Group II (adrenalectomy only) demonstrated that both the alpha and beta adrenergic effect occurred during elevated CSF pressure and indicated the alpha adrenergic stimulation is dependent on an intact sympathetic nervous system but is independent of the adrenal. The beta adrenergic effect seems independent of both an intact sympathetic nervous system and the adrenals. Since the alpha adrenergic effect of increased aortic pressure was absent in Group I (adrenalectomy and ganglionic blockade) and present in Group II (adrenalectomy only), it is probably neurogenically mediated. Group I (studied acutely after adrenalectomy) is not comparable to Group II (studied 17 ± 2 days after adrenalectomy) but Group I did demonstrate a beta adrenergic response of increased

cardiac output and decreased peripheral resistance similar to that in animals previously studied with intact adrenals, ganglionic blockade and alpha adrenergic blockade.<sup>2</sup>

Therefore the Cushing reflex consists of a dual mechanism for the alpha adrenergic component. First the adrenals are necessary to provide a vasoconstrictor agonist that affects denervated skeletal musculature (Group III A). Secondly a neurogenically mediated component is present since the alpha adrenergic effect of increased systemic blood pressure will occur in the adrenalectomized animal with intact sympathetic nervous system (Group I) but will not occur in the adrenalectomized animals with ganglionic blockade (Group I). Also in the adrenalectomized dog the innervated muscle (Group III C) responded dramatically to elevated CSF pressure with no response in the denervated preparation (Group III B).

The expected beta adrenergic effect<sup>2</sup> of elevated cerebrospinal fluid pressure, increased cardiac output or decreased systemic vascular resistance seems independent of the adrenals and the sympathetic nervous system because it is detectable in adrenalectomized dogs with or without ganglionic blockade (Groups I and II). Preliminary studies demonstrated responsiveness of the denervated gracilis muscle preparation to isoproterenol. Since gracilis muscle resistance did not change with elevated CSF pressure in animals with intact adrenals and alpha adrenergic blockade (Group IV), it is assumed no significant circulating vasodilator (beta adrenergic effect) of the denervated skeletal muscle vasculature is present. However, total systemic vascular resistance decreased in Group I (adrenalectomy and ganglionic blockade) and also in animals previously studied with intact adrenals with and without ganglionic blockade and alpha adrenergic blockade.<sup>2</sup> This probably reflects dilation of vascular beds other than skeletal muscle. With alpha adrenergic blockade the beta adrenergic effect may only represent withdrawal of peripheral alpha adrenergic vasoconstrictor tone. However, a beta adrenergic effect occurred in Group I during ganglionic blockade in the absence of specific alpha adrenergic blockade.

The specific origin of a circulating beta adrenergic agonist is open to speculation. It is probably not neuronally released since Glick and co-workers<sup>23</sup> have shown that neuronally released

from the control period during 5 and 10 minutes of CSF pressure 200 mm Hg respectively. In these animals with intact adrenals it is of particular interest that  $21 \pm 17$  seconds (mean  $\pm$  SD) were required for mean aortic pressure to increase to 200 mm Hg after CSF pressure was increased to 200 mm Hg. In contrast  $48 \pm 11$  seconds elapsed before any detectable increase from control was noted in the denervated gracilis muscle perfusion pressure and  $4.6 \pm 3.6$  minutes elapsed before the gracilis muscle perfusion pressure reached a maximum.

In the animals with beta adrenergic blockade, denervated gracilis muscle preparation and adrenalectomy (Group III B) control aortic pressure ( $131 \pm 4$  mm Hg) increased significantly during 5 minutes CSF pressure 200 mm Hg. There was no significant change in the resistance of the denervated gracilis muscle.

In Group III C (beta adrenergic blockade, adrenalectomy, innervated gracilis muscle), control aortic pressure ( $125 \pm 19$  mm Hg) increased significantly during 5 minutes CSF pressure 200 mm Hg. Gracilis muscle resistance increased significantly during 5 and 10 minutes CSF pressure 200 mm Hg. The aortic pressure and gracilis muscle resistance began to increase about the same time (18 to 30 seconds) after CSF pressure was increased to 200 mm Hg. Aortic pressure usually reached a maximal value in 14 to 64 seconds, whereas the gracilis muscle resistance showed a progressive increase over 3 to 45 minutes up to 10 minutes.

Group IV (alpha adrenergic blockade and intact adrenals) aortic pressure demonstrated a significant decrease during 5 and 10 minutes of CSF pressure 200 mm Hg from  $105 \pm 13$  mm Hg in the control period. There was no change in resistance of the gracilis muscle.

Arterial blood for all dogs in the control period demonstrated pH  $7.39 \pm 0.03$ ,  $P_{aCO_2}$   $40 \pm 3$  mm Hg and  $P_{aO_2}$   $87 \pm 7$  mm Hg. At the conclusion of 10 minutes CSF pressure 200 mm Hg, arterial blood showed pH  $7.33 \pm 0.04$ ,  $P_{aCO_2}$   $41 \pm 5$  mm Hg and  $P_{aO_2}$   $83 \pm 8$  mm Hg.

## Discussion

Cushing in 1901<sup>1</sup> demonstrated a pressor response to elevated intracranial pressure. Subsequent investigators considered several mechanisms including a humoral vasopressor in the chick,<sup>2</sup> cerebral ischemia,<sup>3,4</sup> vasoconstriction<sup>5</sup>

neurohumoral stimulation with a phasic response of systemic blood pressure in dogs and rabbit myocardial inotropic response<sup>6</sup> and shunting.<sup>7</sup> Mechanical compression of the rat brain produces a pressor response not altered by adrenalectomy or bilateral cervical vagotomy.<sup>8</sup> A receptive area in the lower brainstem possibly mediates the Cushing response. In 1970 the Cushing response (reflex) was clearly separated into alpha and beta adrenergic components. This study was initiated to determine the etiology of these alpha and beta effects.

The animals with the denervated and perfused gracilis muscle preparation, beta adrenergic blockade and intact adrenals (Group III A) demonstrated an increase in resistance of the gracilis muscle preparation indicating a circulating vasoconstrictor of skeletal muscle. The aortic pressure also increased significantly and could be caused by either a humoral agonist or neurogenic stimulation. The significant time lag between aortic pressure elevation and elevation of the gracilis muscle perfusion pressure is indicative of a circulating vasoconstrictor that is delayed by the external pump that perfuses the gracilis muscle preparation.

In contrast the animals with the denervated, perfused gracilis muscle preparation, beta adrenergic blockade and no adrenals (Group III B) demonstrated an increased aortic pressure but no change in gracilis muscle perfusion pressure or resistance. Therefore the adrenals appear to be the source of the alpha adrenergic agonist affecting the denervated gracilis muscle since any increase in resistance of the gracilis muscle is absent in the adrenalectomized dog with beta adrenergic blockade. The increase in aortic pressure in both Group III A and B is probably neurogenic and nonadrenal in origin.

The neurogenic component of the Cushing reflex is demonstrated in Group III C (no adrenals, beta adrenergic blockade and innervated gracilis muscle). In contrast to the lack of change in the denervated gracilis muscle resistance in Group III B, Group III C demonstrated a marked increase in gracilis muscle resistance.

Group I animals with ganglionic blockade studied acutely after adrenalectomy demonstrated changes similar to those previously reported in animals with intact adrenals, ganglionic blockade and alpha adrenergic blockade.

- 19 Chen H I, Sun M C, and Chai, C Y Pulmonary edema and hemorrhage resulting from cerebral compression *Am J Physiol* 224 193 1973
- 20 Doba N and Reis D J Localization within the lower brain stem of a receptive area mediating the pressor response to increased intracranial pressure (the Cushing response) *Brain Res* 47 487 1972
- 21 Chalmers J P Brain amines and models of experimental hypertension *Circ Res* 36 469 1975
- 22 Neely W A and Youmans J R Anoxia of canine brain without damage *JAMA* 183 1045 1963
- 23 Zimmer R, Lang R, and Oberdorster G Focal ischemic reactive hyperemia of the isolated perfused brain of the dog *Stroke* 3 328 331 1971
- 24 Ramwell P W and Shaw J E Spontaneous and evoked release of prostaglandins from cerebral cortex of anesthetized cats *Am J Physiol* 211 125 1966
- 25 Vogt M Release from brain tissue of compounds with possible transmitter function. Interaction of drugs with these substances *Br J Pharmacol* 37 375 1969
- 26 Doba N and Reis D J Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat *Circ Res* 32 584 1973
- 27 Flück G, Epstein S F, Wechsler A S et al Physiological differences between the effects of neuronally released and blood borne norepinephrine on beta adrenergic receptors in the arterial bed of the dog *Circ Res* 21 217 1967
- 28 Boerth R C, Ryan M J and Brody M J Pharmacologic blockade of reflex vasodilatation. Effects on postulated neurohumoral mechanisms *J Pharmacol Exp Ther* 172 52 1970
- 29 Lefkowitz R J Beta adrenergic receptors: recognition and regulation *N Engl J Med* 295 323 1976
- 30 Hughes R Haemodynamic effects of tubocurarine, gallamine and suxamethonium in dogs *Br J Anaesth* 42 928 1970
- 31 Rathbun F J and Hamilton J T Effect of gallamine on cholinergic receptors *Can Anaesth Soc J* 17 574 1970
- 32 Bergamaschi M, Shanks R G, Caravaggi A M, et al A comparison of the cardiovascular actions of four adrenergic  $\beta$  receptor blocking agents in resting conscious dogs *Am Heart J* 82 338 1971
- 33 Nakano J and Kusakari T Effect of beta adrenergic on the cardiovascular dynamics *Am J Physiol* 210 833 1966
- 34 Barrett A M A comparison of the effects of ( $\pm$ ) propranolol and (+) propranolol in anesthetized dogs  $\beta$  receptor blocking and haemodynamic action *J Pharm Pharmacol* 21 241 1969

norepinephrine does not have access to beta adrenergic receptors in contrast to injected norepinephrine. Although the reuptake of neuronally released norepinephrine may be inhibited by phenoxbenzamine, it is doubtful this permits access of neuronally released norepinephrine to beta adrenergic receptors. It is also possible some autonomic pathways are invulnerable to ganglionic blockade. An adrenal source seems excluded by the present study but brain amines<sup>1</sup> or nonadrenal chromaffin tissue might be a consideration.

A dopaminergic response is an unlikely explanation for the Cushing response since alpha and beta adrenergic antagonists are relatively ineffective in blocking this response. Parasympathetic activity is reasonably excluded since gallamine triethiodide has significant vagolytic effects.<sup>11</sup> Intravenous propranolol in dogs 0.2 to 0.25 mg/Kg effectively blocks changes induced by isoproterenol.<sup>12</sup> However in addition to beta receptor blocking properties propranolol has nonspecific effects that would be similar in Group III A, B and C.<sup>13</sup>

### Summary

The cardiovascular effects of elevated cerebrospinal fluid (CSF) pressure were studied in adrenalectomized dogs with and without ganglionic blockade. A significant increase in vascular pressures and cardiac output occurred in those without ganglionic blockade but was absent or markedly blunted in those with ganglionic blockade. This indicated that an intact sympathetic nervous system was required for the pressor response to elevated cerebrospinal fluid pressure but the adrenals were not required. A beta adrenergic effect was noted in dogs with ganglionic blockade and adrenalectomy.

The effects of elevated CSF pressure were also studied using a perfused gracilis muscle preparation in 12 animals with beta adrenergic blockade with and without adrenalectomy. Animals with intact adrenals and denervated gracilis muscle showed an increase in aortic pressure and gracilis muscle resistance. Adrenalectomized animals with innervated gracilis muscle demonstrated an increase in aortic pressure and gracilis muscle resistance. Elevated CSF pressure with intact adrenals and alpha adrenergic blockade demonstrated a decrease in aortic pressure but no change in gracilis muscle resistance.

The presence of a nonadrenal circulating beta agonist that increases cardiac output and decreases peripheral vascular resistance is indicated by these studies. Also the Cushing reflex involves an adrenal alpha adrenergic component affecting skeletal muscle resistance and another alpha adrenergic component dependent on an intact sympathetic nervous system.

### REFERENCES

1. Cushing H. Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. *Johns Hopkins Hosp Bull* 12:290, 1901.
2. Ducker T B and Simmons R L. Increased intracranial pressure and pulmonary edema. *J Neurosurg* 28:118, 1968.
3. Gonzalez N C and Overman J. Cardiopulmonary responses to uniformly elevated CSF pressure. *J Trauma* 13:727, 1973.
4. Richardson T Q, Farnoso J D and Pugh C O. Effect of acutely elevated intracranial pressure on cardiac output and other circulatory factors. *J Surg Res* 5:318, 1965.
5. Troupp H and Vapiraitis M. Intracranial pressure in the final stages of a severe brain injury. *Acta Neurochir* 25:189, 1971.
6. Norrme H and Magnes B. Intracranial pressure in patients with ruptured saccular aneurysm. *J Neurosurg* 36:537, 1972.
7. Brashear R E and Pamintuan R L. Inert vs. pulmonary diffusing capacity and elevated cerebrospinal fluid pressure. *J Appl Physiol* 30:811, 1971.
8. Brashear R E and Ross J C. Hemodynamic effects of elevated cerebrospinal fluid pressure: Alterations with adrenergic blockade. *J Clin Invest* 49:171, 1970.
9. Brashear R F and Ross J C. Circulating beta adrenergic stimulator during elevated cerebrospinal fluid pressure. *Arch Intern Med* 127:748, 1971.
10. Ballard D R, Aboulod F M and Mayer H F. Release of a humoral vasodilator substance during neurogenic vasodilatation. *Am J Physiol* 219:141, 1970.
11. Heitz D C and Brody M J. Possible mechanism of histamine release during active vasodilatation. *Am J Physiol* 228:131, 1975.
12. Winer B J. Statistical principles of experimental design. New York, 1962. McGraw Hill Book Company, p 81.
13. Rodbard S, Reyes M, Minnichi C et al. Neurohumoral transmission of the pressor response to intracranial compression. *Am J Physiol* 176:711, 1974.
14. Cusson A C. Acute hypertension in dogs with cerebral ischemia. *Am J Physiol* 154:4, 1914.
15. Brown F K. Cardiovascular effects of acutely raised intracranial pressure. *Am J Physiol* 185:310, 1953.
16. Rodbard S and Stone W. Pressure mechanisms induced by intracranial compression. *Circulation* 12:1, 1955.
17. Ducker T B, Simmons R L and Anferon R W. Increased intracranial pressure and pulmonary edema III. The effect of increased intracranial pressure on the cardiovascular hemodynamics of chimpanzees. *J Neurosurg* 29:47, 1968.
18. Brimman J R and Duker T B. Pulmonary venous and splanchnic circulatory responses to increased intracranial pressure. *Ann Surg* 169:70, 1969.

- 19 Chen H I, Sun S C and Chai C Y Pulmonary edema and hemorrhage resulting from cerebral compression *Am J Physiol* 224 723 1973
- 20 Doba N and Reis D J Localization within the lower brain stem of a receptive area mediating the pressor response to increased intracranial pressure (the Cushing response) *Brain Res* 47 487 19 7
- 21 Chalmers J P Brain amines and models of experimental hypertension *Circ Res* 36 469 19 5
- 22 Neely W A and Loumans J H Anoxia of canine brain without damage *JAMA* 183 1080 1963
- 23 Zimmer R, Lang R and Oberdorster G Post ischemic reactive hyperemia of the isolated perfused brain of the dog *Strokers Arch* 328 33 1971
- 24 Ramwell P W and Shaw J E Spontaneous and evoked release of prostaglandins from cerebral cortex of anesthetized cats *Am J Physiol* 211 120 1966
- 25 Vingt M Release from brain tissue of compounds with possible transmitter function Interaction of drugs with these substances *Br J Pharmacol* 37 575 1969
- 26 Doba N and Reis D J Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat *Circ Res* 32 584 19 3
- 27 Glick G, Epstein S E, Wechsler A S et al Physiological differences between the effects of neuronally released and blood borne norepinephrine on beta adrenergic receptors in the arterial bed of the dog *Circ Res* 21 217 1967
- 28 Boerth R C, Ryan M J, and Brody M J Pharmacologic blockade of reflex vasodilatation Effects on postulated neurohumoral mechanisms *J Pharmacol Exp Ther* 172 59 1970
- 29 Lefkowitz R J Beta adrenergic receptors recognition and regulation *N Engl J Med* 295 373 1976
- 30 Hughes R Haemodynamic effects of tubocurarine, gallamine and suxamethonium in dogs *Br J Anaesth* 42 928 19 0
- 31 Rathbun F J and Hamilton J T Effect of gallamine on cholinergic receptors *Can Anaes Soc J* 17 574 1970
- 32 Bergamaschi M, Shanks R G, Caravaggi A M et al A comparison of the cardiovascular actions of four adrenergic  $\beta$  receptor blocking agents in resting conscious dogs, *AM HEART J* 82 338 1971
- 33 Nakano J, and Kusakari T Effect of beta adrenergic on the cardiovascular dynamics, *Am J Physiol* 210 R33 1967
- 34 Barrett A M A comparison of the effects of ( $\pm$ ) propranolol and (+) propranolol in anesthetized dogs  $\beta$  receptor blocking and haemodynamic action *J Pharm Pharmacol* 21 241 1969



norepinephrine does not have access to beta adrenergic receptors in contrast to injected norepinephrine. Although the reuptake of neuronally released norepinephrine may be inhibited by phenoxylbenzamine, it is doubtful this permits access of neuronally released norepinephrine to beta adrenergic receptors. It is also possible some autonomic pathways are invulnerable to ganglionic blockade. An adrenal source seems excluded by the present study but brain amines or nonadrenal chromaffin tissue might be a consideration.

A dopaminergic response is an unlikely explanation for the Cushing response since alpha and beta adrenergic antagonists are relatively ineffective in blocking this response. Parasympathetic activity is reasonably excluded since gallamine triethiodide has significant vagolytic effects.<sup>11</sup> Intravenous propranolol in dogs 0.2 to 0.25 mg/Kg effectively blocks changes induced by isoproterenol.<sup>12</sup> However, in addition to beta receptor blocking properties, propranolol has nonspecific effects that would be similar in Group III A, B, and C.

### Summary

The cardiovascular effects of elevated cerebrospinal fluid (CSF) pressure were studied in adrenalectomized dogs with and without ganglionic blockade. A significant increase in vascular pressures and cardiac output occurred in those without ganglionic blockade but was absent or markedly blunted in those with ganglionic blockade. This indicated that an intact sympathetic nervous system was required for the pressor response to elevated cerebrospinal fluid pressure but the adrenals were not required. A beta adrenergic effect was noted in dogs with ganglionic blockade and adrenalectomy.

The effects of elevated CSF pressure were also studied using a perfused gracilis muscle preparation in 12 animals with beta adrenergic blockade with and without adrenalectomy. Animals with intact adrenals and denervated gracilis muscle showed an increase in aortic pressure and gracilis muscle resistance. Adrenalectomized animals with innervated gracilis muscle demonstrated an increase in aortic pressure and gracilis muscle resistance. Elevated CSF pressure with intact adrenals and alpha adrenergic blockade demonstrated a decrease in aortic pressure but no change in gracilis muscle resistance.

The presence of a nonadrenal circulating beta agonist that increases cardiac output and decreases peripheral vascular resistance is indicated by these studies. Also the Cushing reflex involves an adrenal alpha adrenergic component affecting skeletal muscle resistance and another alpha adrenergic component dependent on an intact sympathetic nervous system.

### REFERENCES

1. Cushing H. Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. *Johns Hopkins Hosp Bull* 12:290, 1901.
2. Duckert T B and Simmons R L. Increased intracranial pressure and pulmonary edema. *J Neurosurg* 28:118, 1968.
3. Gonzalez N C and Overman J. Cardiopulmonary responses to uniformly elevated CSF pressure. *J Trauma* 13:727, 1973.
4. Richardson T Q, Fermojo J D, and Pugh C O. Effect of acutely elevated intracranial pressure on cardiac output and other circulatory factors. *J Surg Res* 5:318, 1965.
5. Troupp H and Vapalahti M. Intracranial pressure in the final stages of a severe brain injury. *Acta Neurochir* 25:189, 1971.
6. Norries H and Maigne B. Intracranial pressure in patients with ruptured saccular aneurysm. *J Neurosurg* 36:537, 1972.
7. Brashear R E and Pimentum R L. Increased pulmonary diffusing capacity and elevated cerebrospinal fluid pressure. *J Appl Physiol* 30:844, 1971.
8. Brashear R E and Ross J C. Hemodynamic effects of elevated cerebrospinal fluid pressure. Alterations with adrenergic blockade. *J Clin Invest* 49:1324, 1970.
9. Brashear R E and Ross J C. Circulating beta adrenergic stimulator during elevated cerebrospinal fluid pressure. *Arch Intern Med* 127:748, 1971.
10. Billard D R, Abboud F M, and Maxam H F. Release of a humoral vasodilator substance during neurogenic vasodilatation. *Am J Physiol* 219:141, 1970.
11. Heitz D C and Brody M J. Possible mechanism of histamine release during active vasodilatation. *Am J Physiol* 228:1331, 1975.
12. Winer B J. Statistical principles of experimental design. New York, 1962. McGraw Hill Book Company, p. 63.
13. Hubbard S, Reyes M, Mininni T, et al. Neurohumoral transmission of the pressor response to intracranial compression. *Am J Physiol* 176:311, 1973.
14. Cusum A C. Acute hypertension in dogs with cerebral ischemia. *Am J Physiol* 154:4, 1958.
15. Brown F K. Cardiovascular effects of acutely raised intracranial pressure. *Am J Physiol* 185:110, 1953.
16. Billard S and Stone W. Pressure mechanisms induced by intracranial compression. *Circulation* 12:5, 1955.
17. Duckert T B, Simmons R L, and Anderson R W. Increased intracranial pressure and pulmonary edema. III. The effect of increased intracranial pressure on the cardiovascular hemodynamics of chimpanzees. *J Neurosurg* 29:4, 1968.
18. Herman I R, and Duckert T B. Eulmonary hypertension and systemic circulatory response to increased intracranial pressure. *Ann Surg* 169:710, 1970.





of 30 mg/kg and it was placed in oxygenated Tyrode's solution composed of (mM) NaCl 147 KCl 4.0 CaCl<sub>2</sub> 1.8 MgCl<sub>2</sub> 0.5 dextrose 5.5 NaH<sub>2</sub>PO<sub>4</sub> 1.5 NaHCO<sub>3</sub> 4.5

Preparations of both the LBB and RBB systems obtained from the canine heart were immersed in a single tissue bath. The chamber was perfused with Tyrode's solution equilibrated with 100 per cent O<sub>2</sub>. The temperature of the bath was kept between 36 and 36.5 °C.

Transmembrane action potentials were recorded through machine pulled glass microelectrodes filled with 3M KCl and having resistances between 10 and 30 megohms. Signals from the microelectrodes were fed to amplifiers (MZ 4 Nihonkoden and M701 W. P. Instruments Inc.) and the outputs of these amplifiers were displayed on oscilloscopes (VC 7 Nihonkoden and 5103N Tektronix). The transmembrane signals were recorded photographically from the oscilloscope screens.

**Tissue preparations** Fig. 1 shows the preparations of the LBB and RBB systems (stained with Lugol's solution) used in the current experiments. The specimen of the LBB system is shown in the upper panel of the figure. The main left bundle emerges with a band-like structure below the aortic ring and it courses down the septum a few millimeters before the main LBB bifurcates into the anterior (AF) and posterior fascicles (PF) which are attached to the apical portions of the papillary muscles. A profuse subendocardial network of the mid-septal Purkinje fibers (SEP) is distributed throughout the septal surface bordered by two major fascicles.

The preparation of the RBB system consists of the main RBB in the right upper septum and its subsequent two or three false tendons which terminate in the free wall (lower panel Fig. 1). To study APD and refractory periods along this pathway on the right side of the conduction system, the right ventricular septal muscle was separated from the free wall or anterior papillary muscle (PM). As shown in diagrams of the RBB specimen in Figs. 2 and 3, consequently these muscle masses were bridged by a single strand of the RBB.

**Stimulation of the preparations** In each experiment a pair of preparations of the right and left conducting systems obtained from a dog heart were stimulated simultaneously using the same stimulator through two pairs of bipolar electrodes

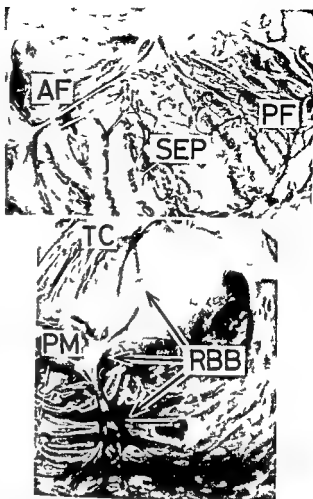


Fig. 1 A pair of preparations of the left bundle branch system (top panel) and right bundle branch system (bottom panel) isolated from the same canine heart (stained with Lugol's solution). In the specimen from the LBB (top) the septal muscle was rather large (about 3 × 5 cm) and it included the septal Purkinje fibers (SEP) the anterior (AF) and posterior (PF) fascicles. The RBB specimen (bottom) consisted of the main RBB with its attached septal muscle and false tendons which terminated in ventricular free wall. RBB = right bundle branch. TC = tricuspid valve. PM = anterior papillary muscle.

on each proximal portion of the RBB and LBB. The specimens were driven at a basic cycle length of 7.0 msec (80 times/minute) using a driving stimulus (S1) which was two times the diastolic threshold in intensity and 1 msec in duration.

In order to determine the functional refractory period (FRP) a test stimulus (S2) was delivered through the same electrodes after every eighth driving stimulus. The minimum interval between the response (R1) to S1 and the response (R2) to S2 was defined as the FRP in each of the right and left ventricular conduction systems.

# Functional properties of the left septal Purkinje network in premature activation of the ventricular conduction system

Nobuyuki Iwamura M D  
Itsuo Kodama M D  
Takeshi Shimizu, M D  
Yukio Hirata M D  
Junji Toyama, M D  
Kazuo Yamada, M D  
Nagoya Japan

In relatively recent *in vivo* or *in vitro* experiments on the canine heart<sup>1-3</sup> several investigators have suggested that the left bundle branch (LBB) system has three rather than two separate divisions i.e. a trifascicular concept of the left conducting system consisting of the septal Purkinje fibers besides the anterior (AF) and posterior (PF) fascicles. Very lately, in addition, Lazzara and co workers<sup>4</sup> have reported that the septal Purkinje fibers of the LBB system which were termed interior fibers by them, have significantly shorter action potential durations (APD) and refractory periods than the right bundle branch (RBB) the AF and PF of the LBB system. In the series of our experiments apart from the work of Lazzara and colleagues<sup>4</sup> we compared the APD (80 per cent of repolarization time) and functional refractory period (FRP) between the canine left and right conduction systems in order to elucidate the electrophysiological mechanism underlying aberrant ventricular conduction. As the result of our experiments in agreement with their study<sup>4</sup> we have found that both the APD and the FRP of the mid septal Purkinje fibers in the LBB system are significantly shorter than those of the other three

conduction pathways, and have reported previously<sup>5</sup> that the electrophysiological properties of the septal Purkinje fibers might contribute to the higher incidence of RBB block in ventricular aberrant conduction of supraventricular premature beats.

Since however septal Purkinje fibers near the main LBB could not be clearly differentiated from conducting fibers of the AF and PF in the subendocardium which were named anterior and posterior border fibers by Lazzara and colleagues<sup>4</sup> it seemed quite essential to confirm the functional independence of the septal Purkinje network serving as a conduction pathway for premature impulses delivered to the main LBB. In the present study therefore we elucidated the premature activation sequences of the left conducting tissue and ordinary ventricular muscle when premature stimuli were applied to the main LBB using a relatively large preparation including all three major pathways of the left conduction system. As a result it has been demonstrated that the septal Purkinje fibers have functional significance for conduction of premature impulses and there are not such definite gate cells in this pathway as Myerburg and colleagues<sup>6</sup> have proposed previously.

## Methods

Experiments were performed on isolated cardiac tissue obtained from mongrel dogs. The heart was removed from the dog after anesthetizing it with sodium pentobarbital administered at a rate

From the Division of Circulation and Respiration, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan.  
Received for publication Dec. 29, 1976.

Accepted for publication Mar. 4, 1977.

Reprint requests: Nobuyuki Iwamura, M.D., Division of Circulation and Respiration, Research Institute of Environmental Medicine, Nagoya University, 464 Furo-cho, Chikusa-ku, Nagoya, Japan.

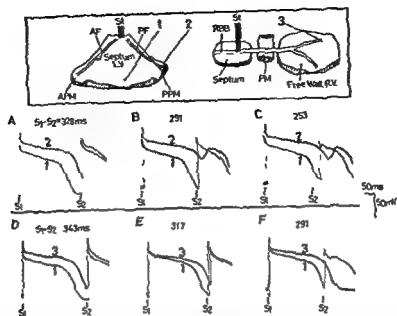


Fig. 3. Diagrams of premature responses of Purkinje fibers between the LBB and RBB systems. Action potentials were recorded from three sites: (1) the lower third of the left ventricular central septum; (2) the terminations of the PF and (3) the RBB. Action potentials of driven and premature responses were recorded simultaneously from the sites of (1) and (2) (panels A, B and C) and from the sites of (1) and (3) (panels D, E and F) at various coupling (S-S) intervals. Note that the premature response of the septal Purkinje fiber was elicited at an S-S interval of .53 msec, though the terminal Purkinje cells of the PF and the RBB responded only abortively or did not respond to test stimuli at longer coupling intervals.

thereafter they form the false tendons (solid lines) which terminate in ventricular muscle. In these conduction pathways we observed a progressive lengthening of APD with increasing distance from the main bundle branches to the false tendons and an area of maximum APD (max APD) was found at the false tendon. On the other hand the septal Purkinje fibers of the LBB system (SFP) are blanketing the subendocardium from the origin to their termination in ventricular muscle (interrupted line). In this specimen there was a tendency to shorter durations with distance progression along the approximately intermediate septal surface between the AF and PF. As a general rule however it was almost impossible to clearly discriminate the septal Purkinje fibers from conducting fibers of the AF or PF within several millimeters from the main LBB. Although there was a trend toward longer durations of action potentials recorded from the interior septal surface along the AF and PF, the septal Purkinje fibers had apparently shorter action potentials than the other three conduction pathways at almost all sites approximately equidistant from the main bundle branches.

In a total of 18 experiments, we compared the

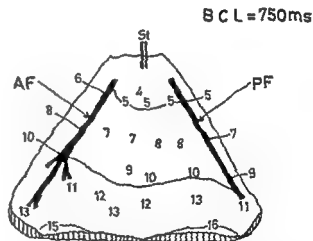


Fig. 4. An isochronous map showing the sequence of normal activation of the left conducting system. The left preparation was driven at a basic cycle length (BCL) of 750 msec through a pair of bipolar surface electrodes (S1) on the main LBB. Numbers in the diagram indicate activation times (msec.) of the Purkinje fiber.

maximum APD (max APD) among the four conduction pathways in a pair of the left and right specimens which were isolated from the same canine heart. The results are shown in the left column of Table I. The number of experi-



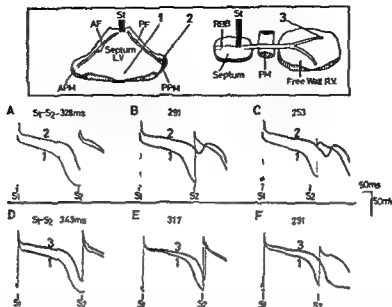


Fig 3 Diagrams of premature responses of Purkinje fibers between the LBB and RBB systems. Action potentials were recorded from three sites: (1) the lower third of the left ventricular central septum; (2) the terminations of the PF and (3) the RBB. Action potentials of driven and premature responses were recorded simultaneously from the sites of (1) and (2) (panels A, B and C) and from the sites of (1) and (3) (panels D, E and F) at various coupling (S-S) intervals. Note that the premature response of the septal Purkinje fiber was elicited at an S-S interval of 2-3 msec, though the terminal Purkinje cells of the PF and the RBB responded only abortively or did not respond to test stimuli at longer coupling intervals.

thereafter they form the false tendons (solid lines) which terminate in ventricular muscle. In these conduction pathways we observed a progressive lengthening of APD with increasing distance from the main bundle branches to the false tendons and an area of maximum APD (max APD) was found at the false tendon. On the other hand, the septal Purkinje fibers of the LBB system (SFP) are blanketing the subendocardium from the origin to their termination in ventricular muscle (interrupted line). In this specimen there was a tendency to shorter durations with distance progression along the approximately intermediate septal surface between the AF and PF. As a general rule, however, it was almost impossible to clearly discriminate the septal Purkinje fibers from conducting fibers of the AF or PF within several millimeters from the main LBB. Although there was a trend toward longer durations of action potentials recorded from the interior-septal surface along the AF and PF, the septal Purkinje fibers had apparently shorter action potentials than the other three conduction pathways at almost all sites approximately equidistant from the main bundle branches.

In a total of 18 experiments, we compared the

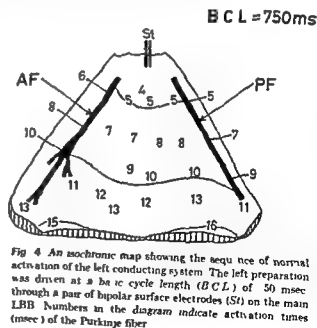


Fig 4 An isochronic map showing the sequence of normal activation of the left conducting system. The left preparation was driven at a basic cycle length (BCL) of 50 msec through a pair of bipolar surface electrodes (S1) on the main LBB. Numbers in the diagram indicate activation times (msec) of the Purkinje fiber.

maximum APD (max APD) among the four conduction pathways in a pair of the left and right specimens which were isolated from the same canine heart. The results are shown in the left column of Table I. The number of exper-



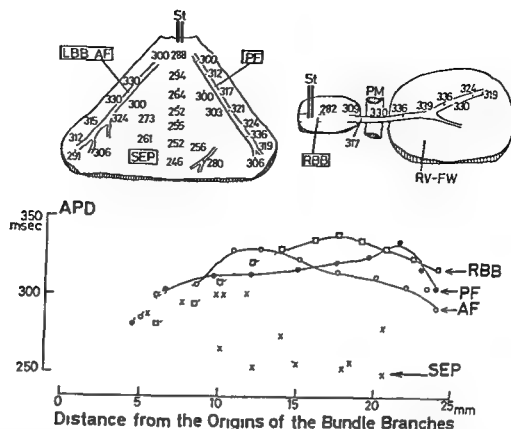


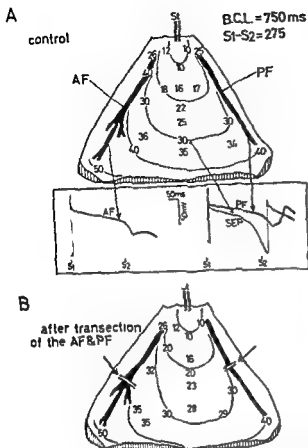
Fig 2 Action potential durations (APD) of Purkinje fibers mapped along the courses of a pair of preparations of the LBB and RBB systems. In upper panels numbers in the diagrams indicate 80 per cent level of repolarization time in msec. In the lower panel the graph was drawn to represent a relation between the values of APD obtained and distance (mm) of recording sites from the origins of the bundle branches on the ventricular septal surface. APD measured at the subendocardial Purkinje fiber was connected by interrupted lines and APD at the false tendon was linked by solid lines. At almost all comparable levels in the ventricular conducting systems the APD of the septal Purkinje fibers (SEP) of the LBB system (marked by x) was consistently shorter than that of the RBB (open square), the AF (open circle) and the PF (filled circle) of the LBB system. LBB AF = the anterior fascicle of the LBB system; PF = the posterior fascicle; SEP = the septal Purkinje fibers; RV FW = free wall of the right ventricle; St = bipolar electrodes for stimulation.

In the left preparation stimulation of the Purkinje fiber in the main LBB devoid of the adjacent muscle was confirmed (Figs 4 and 6A). Stimulation (St) delivered through a pair of bipolar surface electrodes on the origin of the LBB allowed propagation of activation of Purkinje fibers from base to apex along the AF, PF, and septal Purkinje network (Fig 4). The earliest muscle activation on the other hand was approximately at the lower third of the septum between the papillary muscles and the general sequence of the ordinary ventricular muscle was from apex to base (Fig 6A).

## Results

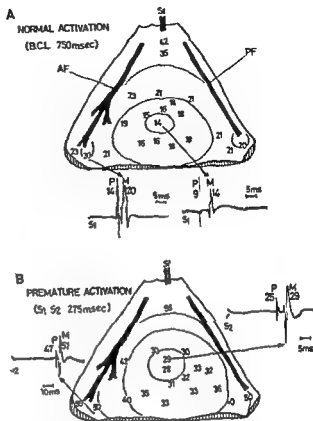
**Comparison of action potential durations between the LBB and RBB systems.** In each of 18 experiments, action potentials of Purkinje fibers were recorded from 15 to 20 points along each of the courses of the following four conduction

pathways in a pair of the left and right specimens which were obtained from the same canine heart: (1) the conduction pathway consisting of the main RBB and its subsequent false tendons which terminate in the ventricular free wall (RBB), (2) the anterior fascicle of the LBB system (LBB AF), (3) the posterior fascicle (LBB PF), and (4) the septal Purkinje fibers on the left septal surface between the AF and PF (LBB SEP). Fig 2 shows action potential durations (APD) obtained in this way in a pair of typical preparations. In the upper panel of this figure numbers in diagrams of the specimens indicate APD (msec). The values of the APD are plotted against distance (mm) from the origin of the bundle branch on the surface of the interventricular septum (lower panel Fig 2). The RBB, AF, and PF of the LBB system are subendocardial structures (interrupted lines in the lower graph of Fig 2) within 5 to 15 mm from their origins and



**Fig 5** An isochronic map showing the sequence of premature activation of the left conducting tissue in the same specimen as Fig 4 indicated (panel A). Numbers in the diagram indicate activation times (msec) of the Purkinje fiber in response to a premature impulse ( $S_1$ ) delivered to the main LBB at an S-S interval of 275 msec, which was nearly equal to refractory periods of the AF and PF. The sequence of Purkinje activation was from base to apex along the mid-septum. Records in insets show driven and premature action potentials of the AF, the PF, and the septal Purkinje fiber at this critical coupling interval. Panel B shows the premature activation sequence of the conducting fibers at the same S-S interval after transection of the false tendons of the AF and PF. The incision of these fascicles produced no significant changes in premature activation times.

delay of conduction (42 msec) even at an S-S interval of 253 msec and repolarization of this cell was still nearly complete (panel C Fig 3). As shown in the lower recordings of Fig 3, the terminal Purkinje fiber in the RBB responded to the premature impulse until a coupling interval was shortened to 317 msec (panels D and E Fig 3). The premature response of the cell no longer occurred at an S-S interval of 291 msec (panel F Fig 3).



**Fig 6** Sequential activation of muscle cells of the septal surface in response to a basic stimulus ( $S_1$ ) (panel A) and a premature stimulus ( $S_2$ ) having a coupling interval of 275 msec (panel B). Numbers in the diagrams indicate activation times (msec) after stimulation. The earliest muscle activation was observed at approximately the same region (middle or lower third of the central septum) in both normal and premature activation of the LBB system. Records below and at the sides show bipolar surface electrograms from the anterior papillary muscle and an area at which the initial muscle activation was observed. P = Purkinje activation; M = muscle activation.

**Functional properties of the septal Purkinje fibers in premature activation of the LBB system.** Using a pair of close bipolar electrodes, we measured the activation time of the Purkinje fiber at about 40 points in the left preparation while the main LBB was driven at a basic cycle of 750 msec (80 times/minute). In the isochronic map indicating the normal activation sequence as shown in Fig 4, the left conducting tissue was activated from base to apex forming concentric wave fronts along the major fascicles (the AF and PF) and the septal Purkinje network. Since there were significant differences in the FRP between the septal Purkinje fiber and the false tendons of the AF and PF as shown in Table 1, the pre-

**Table 1** Comparison of the maximum APD (max APD) and the FRP between the left and right conduction pathways

|                 | max APD  | FRP      |
|-----------------|----------|----------|
|                 | (N = 16) | (N = 16) |
| RBB             | 337      | 332      |
| LBB SEP         | 302      | 300      |
| Mean difference | 35 ± 19* | 32 ± 14  |
|                 | (N = 9)  | (N = 9)  |
| LBB AF          | 323      | 315      |
| LBB SEP         | 301      | 289      |
| Mean difference | 22 ± 8*  | 26 ± 14* |
|                 | (N = 15) | (N = 13) |
| LBB PF          | 341      | 336      |
| LBB SEP         | 302      | 297      |
| Mean difference | 39 ± 17* | 39 ± 19  |

Values are mean (± SD) msec of the number of preparations studied (number in parentheses)

\*  $P < 0.005$  (Student's *t* test)

Abbreviations: max APD = the maximum value of action potential durations mapped along the courses of the conduction pathways; FRP = the functional refractory period of the Purkinje fiber measured at the terminations of the conduction pathways; RBB = the right bundle branch; LBB SEP = the septal Purkinje fiber of the left bundle branch system; LBB AF = the anterior fascicle; LBB PF = the posterior fascicle

ments shown (in parentheses) differs because action potentials were recorded from only two or three pathways in several preparations. As shown in the first comparison, the mean values of the max APD of the RBB and the septal Purkinje fiber of the LBB system (LBB SEP) were 337 and 302 msec respectively, and the mean difference in each experiment was  $35 \pm 19$  (± SD) msec. In addition the max APD of the septal Purkinje fiber was significantly shorter than that of the AF and PF of the LBB system and the mean differences were  $22 \pm 8$  and  $39 \pm 17$  msec respectively. These differences (asterisks in Table I) were statistically significant ( $p < 0.005$  Student's *t* test). However we did not find any meaningful difference in the max APD between the RBB and the AF and the PF (these comparisons were omitted in Table I).

**Comparison of functional refractory periods between the LBB and RBB systems.** Using the same specimens as were used to measure APD we determined the FRP at the following four sites in the RBB and LBB systems: the terminations of (1) the RBB (2) the AF and (3) the PF of the LBB system and (4) the lower surface of the midseptum nearly intermediate between the AF

and PF. Since the earliest muscle activation was observed approximately at the junction of the middle and lower thirds of the midseptum (Fig 6A) and the septal Purkinje fiber was therefore assumed to terminate in the ordinary ventricular muscle at this particular region the FRP of the septal Purkinje fiber was measured at the above mentioned site in the septum. Comparison of the FRP was made among the four conduction pathways in the same way as that of the max APD. The right column of Table I represents the results. There was a close relation between each value of the FRP at the four conduction pathways and the max APD of the corresponding courses. The FRP of the septal Purkinje fiber of the LBB system was significantly ( $p < 0.005$ ) shorter than that of the terminal Purkinje cell in the RBB, the AF and PF of the LBB system. However we found no significant differences in the FRP among the false tendons of the RBB, the AF, and PF.

It was suggested that these differences in refractory periods among the pathways would result in significant disparities in premature responses of Purkinje fibers between the left and right conducting systems. Fig 3 shows that this is true. As indicated in the diagrams, action potentials of Purkinje fibers were recorded from three sites in a pair of specimens which were stimulated simultaneously by the same stimulator: the lower third of the left ventricular septum (site 1), the terminations of the PF of the LBB system (site 2) and of the RBB (site 3). At various  $S_1$ - $S_2$  intervals the action potentials of driven and premature responses were recorded simultaneously from the Purkinje fibers in the lower septum and the PF (panels A, B, and C Fig 3) and from the cells in the lower septum and the RBB (panels D, E and F Fig 3).

At an  $S_1$ - $S_2$  interval of 328 msec both the cells in the lower septum and the termination of the PF fully responded to the test impulse ( $S_2$ ) without any delay of conduction of the premature impulse (panel A, Fig 3). At a coupling interval of 291 msec however, the premature action potential of the cell in the PF showed a slow upstroke with some delay of conduction of the test impulse. On the other hand the septal Purkinje fiber was almost fully repolarized at that time and appropriately responded to  $S_2$  without any significant delay (panel B Fig 3). The cell in the lower septum responded to the test impulse with some

the APD and FRP were compared between the LBB and RBB systems. As a result we have found that the maximum APD and the FRP of the septal Purkinje fibers in the LBB system are significantly shorter than those of the RBB, the AF and PF of the LBB system (Table I). These results are in accord with the recent study performed by Lazzara and colleagues. They therein reported that there was a tendency to longer durations of action potentials of interior fibers (septal Purkinje fibers) of the LBB system with distance progression though they observed somewhat greater variability in the APD among these fibers. In our 18 preparations we also observed that the APD of the septal Purkinje fiber greatly varied among recording sites on the septal surface. However we found no consistent relation between the APD of the septal Purkinje fiber and distance of recording sites from the main LBB in the majority of specimens though there was a general tendency to shorter durations of these fibers with increasing distance from the proximal LBB along the approximately intermediate septal surface between the AF and PF in six of 18 preparations as shown in Fig. 2. Such inconsistency between our result and their report seems to be related to the following matters. First it was almost impossible to differentiate the septal Purkinje fibers from the conducting fibers originated from the AF and PF near the proximal LBB since the septal Purkinje fibers are confluent with the subendocardial Purkinje cells of the AF and PF which have been termed the anterior and posterior border fibers by them, forming a fan-shaped structure on the upper septum below the main LBB. Therefore it seems possible that action potentials recorded from the upper septum are actually those of conducting fibers originated from the AF or PF. In most of our preparations (11 out of 18) moreover we observed a general tendency to longer APD at the interior septal surface along the false tendons of the AF and PF than at the central septum. This variation of APD may be ascribed to a rather dense distribution of conducting fibers which branch off directly from the two fascicles. Secondly a profuse network of septal Purkinje fibers consisted of innumerable branches having various thicknesses and sizes from fine thread to strand-like structures after specimens were stained with iodine. As a general tendency we found longer APD in rather thicker branches

than in nearby cells in very thin networks with the aid of a dissecting microscope. In addition longer durations were often obtained from the false tendon-like structure which was formed by septal Purkinje fibers occasionally even on the midseptum. Thus greater variability in APD among recording sites on the septal surface seems to result from such an irregular architecture of the septal Purkinje fibers as described above.

Combining these observations it has been suggested that these septal Purkinje cells have a very complex distribution showing rich interconnections with fibers originated from the AF and PF especially in the vicinity of the main LBB and the interior septal surface along the two fascicles. Therefore it seemed quite indispensable to confirm (1) the functional independence of the septal Purkinje fibers as a conduction pathway for premature impulses in spite of such a complex and irregular architecture of these fibers and (2) the lack of such gate cells in this conduction pathway as Myerburg and colleagues<sup>1</sup> have brought forward. For these purposes we elucidated the activation sequences of the left conducting tissue and ordinary ventricular muscle of the septal surface in response to a premature impulse delivered to the main LBB at a critical coupling interval close to the refractory periods of the AF and PF. In this experiment we observed that the earliest muscle activation by the test impulse occurred at the same area near the junction of the middle and lower thirds of the septum as in normal activation of the LBB system and that the intervals between Purkinje and muscle activation in bipolar surface electrograms recorded from this particular area were almost constant under these two conditions (Fig. 6). Thus it has been demonstrated that the septal Purkinje network provides the quickest pathway for conduction of premature impulses to the septal myocardium and moreover that there is no definite distal gate in this pathway.

It has been reported that action potentials of the anterior septal branch of the RBB have also shorter durations than those of the false tendons on the right side of the conducting system. Relating to the mechanism underlying incomplete RBB block however Hishida reported that selective incisions of the anterior septal or posterior branches of the canine RBB produced no significant change in configuration and duration of QRS complexes on the other hand.

ture activation sequence of the LBB system by the test impulse having a critical coupling interval close to the refractory periods of these fascicles was expected to differ from the normal activation sequence. At an S<sub>1</sub>S<sub>2</sub> interval of 275 msec, which was nearly equal to the refractory periods of the AF and PF, the premature activation time of the left conducting fiber was mapped in the same specimen as Fig 4 indicated (Fig 5A). As shown in this figure, the Purkinje fiber on the left septal surface was activated nearly along the midseptum from the proximal LBB to the apex with additional conduction delay (5 to 35 msec) of the test impulse (S<sub>2</sub>) compared with the normal activation shown in Fig 4. At that time we observed marked delay of conduction of the premature impulse in the major fascicles. In order to verify disparities of premature responses between the septal Purkinje fiber and these false tendons, action potentials were recorded from the terminal Purkinje fibers of the AF and PF and from the septal Purkinje cell in the lower midseptum (insets of Fig 5). The premature action potential of the AF showed only a minor hump like response and that of the PF an abortive depolarization with pronounced conduction delay of the test impulse (S<sub>2</sub>). On the other hand the premature response of the septal Purkinje fiber showed a nearly full sized depolarization rising from the deeper level of the membrane potential resulting in smaller conduction delay (20 msec) of S<sub>2</sub>.

In order to give some definite evidence of the functional significance of the septal Purkinje fibers, after transection of the AF and PF we constructed an isochronic map showing the sequence of premature activation of the left conducting tissue in the same specimen (Fig 5B). The cutting of these two false tendons produced no significant changes in premature activation times of conducting cells even at the papillary muscles in which the major fascicles terminated. At this critical coupling interval (275 msec) therefore the premature impulse was propagated over the entire septal surface through the septal Purkinje network.

Furthermore we elucidated the sequences of normal and premature activation of ordinary ventricular muscle of the septal surface in the same specimen (Fig 6). In response to a driving stimulus (S<sub>1</sub>) delivered to the main LBB the earliest muscle activation was observed at the

junction of the middle and lower thirds of the midseptum (14 to 15 msec after S<sub>1</sub>) and the myocardium of the septal surface was activated in the form of concentric bands around this island. On the other hand muscle activation at the papillary muscles was observed relatively early (20 to 23 msec after stimulation) (Fig 6A). Fig 6B represents the sequence of muscle activation by the test impulse (S<sub>2</sub>) having an S<sub>1</sub>S<sub>2</sub> interval of 275 msec. The initial activation of the septal muscle was observed 28 to 30 msec after S<sub>2</sub> at almost the same area as in normal activation and the muscle activation spread over the entire septal surface forming concentric lines. The papillary muscles consequently, were activated very late (50 to 55 msec after S<sub>2</sub>) compared with normal activation. From these results it was apparent that the septal Purkinje fibers provided the quickest pathway for conduction of the test impulse to the septal myocardium at this critical coupling interval. In the false tendons of the AF and PF however conduction of the premature impulse was accompanied by marked delay because of their longer refractoriness. Thus these fascicles did not function effectively as conduction pathways for S<sub>2</sub> at this coupling interval.

## Discussion

Many investigators<sup>1-6</sup> have reported that the LBB system consists of three major conduction pathways (trifascicular system). Lazzara and colleagues<sup>1</sup> studied the activation sequences of the left conducting tissue and septal myocardium before and after transection of the proximal LBB using rather large specimens isolated from the canine left ventricle. This study indicated the functioning of the septal Purkinje fibers as an independent pathway from the AF and PF in physiological conditions. Several experiments on *in vivo* canine hearts<sup>1,2</sup> suggested that the activation of the left ventricular muscle of the septum is initiated by propagated impulses predominantly through the septal Purkinje fibers. In addition an anatomical study<sup>3</sup> on the canine ventricular special conduction system showed the trifascicular system of the LBB system consisting of the anterior and posterior primary branches and a vast network of fibers extending between the major branches in the LBB system.

In the present study with the purpose of elucidating the mechanism of ventricular aberrant conduction with an RBB block pattern both

the APD and FRP were compared between the LBB and RBB systems. As a result we have found that the maximum APD and the FRP of the septal Purkinje fibers in the LBB system are significantly shorter than those of the RBB, the AF and PF of the LBB system (Table I). These results are in accord with the recent study performed by Iazzara and colleagues. They therein reported that there was a tendency to longer durations of action potentials of interior fibers (septal Purkinje fibers) of the LBB system with distance progression though they observed somewhat greater variability in the APD among these fibers. In our 18 preparations we also observed that the APD of the septal Purkinje fiber greatly varied among recording sites on the septal surface. However we found no consistent relation between the APD of the septal Purkinje fiber and distance of recording sites from the main LBB in the majority of specimens though there was a general tendency to shorter durations of these fibers with increasing distance from the proximal LBB along the approximately intermediate septal surface between the AF and PF in six of 18 preparations as shown in Fig. 2. Such inconsistency between our result and their report seems to be related to the following matters. First it was almost impossible to differentiate the septal Purkinje fibers from the conducting fibers originated from the AF and PF near the proximal LBB since the septal Purkinje fibers are confluent with the subendocardial Purkinje cells of the AF and PF which have been termed the anterior and posterior border fibers by them forming a fan-shaped structure on the upper septum below the main LBB. Therefore it seems possible that action potentials recorded from the upper septum are actually those of conducting fibers originated from the AF or PF. In most of our preparations (11 out of 18) moreover we observed a general tendency to longer APD at the interior septal surface along the false tendons of the AF and PF than at the central septum. This variation of APD may be ascribed to a rather dense distribution of conducting fibers which branch off directly from the two fascicles. Secondly a profuse network of septal Purkinje fibers consisted of innumerable branches having various thicknesses and sizes from fine thread to strand-like structures. After specimens were stained with iodine. As a general tendency we found longer APD in rather thicker branches

than in nearby cells in very thin networks with the aid of a dissecting microscopy. In addition longer durations were often obtained from the false tendon-like structure which was formed by septal Purkinje fibers occasionally even on the midseptum. Thus greater variability in APD among recording sites on the septal surface seems to result from such an irregular architecture of the septal Purkinje fibers as described above.

Combining these observations it has been suggested that these septal Purkinje cells have a very complex distribution showing rich interconnections with fibers originated from the AF and PF especially in the vicinity of the main LBB and the interior septal surface along the two fascicles. Therefore it seemed quite indispensable to confirm (1) the functional independence of the septal Purkinje fibers as a conduction pathway for premature impulses in spite of such a complex and irregular architecture of these fibers and (2) the lack of such gate cells in this conduction pathway as Myerburg and colleagues have brought forward. For these purposes we elucidated the activation sequences of the left conducting tissue and ordinary ventricular muscle of the septal surface in response to a premature impulse delivered to the main LBB at a critical coupling interval close to the refractory periods of the AF and PF. In this experiment we observed that the earliest muscle activation by the test impulse occurred at the same area near the junction of the middle and lower thirds of the septum as in normal activation of the LBB system and that the intervals between Purkinje and muscle activation in bipolar surface electrograms recorded from this particular area were almost constant under these two conditions (Fig. 6). Thus it has been demonstrated that the septal Purkinje network provides the quickest pathway for conduction of premature impulses to the septal myocardium and moreover that there is no definite distal gate in this pathway.

It has been reported that action potentials of the anterior septal branch of the RBB have also shorter durations than those of the false tendons on the right side of the conducting system. Relating to the mechanism underlying incomplete RBB block however Hishida<sup>11</sup> reported that selective incisions of the anterior septal or posterior branches of the canine RBB produced no significant change in configuration and duration of QRS complexes on the other hand.

ture activation sequence of the LBB system by the test impulse having a critical coupling interval close to the refractory periods of these fascicles was expected to differ from the normal activation sequence. At an S<sub>1</sub>S<sub>2</sub> interval of 275 msec which was nearly equal to the refractory periods of the AF and PF the premature activation time of the left conducting fiber was mapped in the same specimen as Fig 4 indicated (Fig 5A). As shown in this figure, the Purkinje fiber on the left septal surface was activated nearly along the midseptum from the proximal LBB to the apex with additional conduction delay (5 to 35 msec) of the test impulse (S<sub>2</sub>), compared with the normal activation shown in Fig 4. At that time, we observed marked delay of conduction of the premature impulse in the major fascicles. In order to verify disparities of premature responses between the septal Purkinje fiber and these false tendons action potentials were recorded from the terminal Purkinje fibers of the AF and PF and from the septal Purkinje cell in the lower midseptum (insets of Fig 5). The premature action potential of the AF showed only a minor hump like response and that of the PF an abortive depolarization with pronounced conduction delay of the test impulse (S<sub>2</sub>). On the other hand the premature response of the septal Purkinje fiber showed a nearly full sized depolarization rising from the deeper level of the membrane potential resulting in smaller conduction delay (20 msec) of S<sub>2</sub>.

In order to give some definite evidence of the functional significance of the septal Purkinje fibers after transection of the AF and PF we constructed an isochronic map showing the sequence of premature activation of the left conducting tissue in the same specimen (Fig 5B). The cutting of these two false tendons produced no significant changes in premature activation times of conducting cells even at the papillary muscles in which the major fascicles terminated. At this critical coupling interval (275 msec) therefore the premature impulse was propagated over the entire septal surface through the septal Purkinje network.

Furthermore we elucidated the sequences of normal and premature activation of ordinary ventricular muscle of the septal surface in the same specimen (Fig 6). In response to a driving stimulus (S<sub>1</sub>) delivered to the main LBB the earliest muscle activation was observed at the

junction of the middle and lower thirds of the midseptum (14 to 15 msec after S<sub>1</sub>) and the myocardium of the septal surface was activated in the form of concentric bands around this island. On the other hand, muscle activation at the papillary muscles was observed relatively early (20 to 23 msec after stimulation) (Fig 6A). Fig 6B represents the sequence of muscle activation by the test impulse (S<sub>2</sub>) having an S<sub>1</sub>S<sub>2</sub> interval of 275 msec. The initial activation of the septal muscle was observed 28 to 30 msec after S<sub>2</sub> at almost the same area as in normal activation and the muscle activation spread over the entire septal surface forming concentric lines. The papillary muscles consequently were activated very late (50 to 55 msec after S<sub>2</sub>) compared with normal activation. From these results it was apparent that the septal Purkinje fibers provided the quickest pathway for conduction of the test impulse to the septal myocardium at this critical coupling interval. In the false tendons of the AF and PF, however, conduction of the premature impulse was accompanied by marked delay because of their longer refractoriness. Thus these fascicles did not function effectively as conduction pathways for S<sub>2</sub> at this coupling interval.

## Discussion

Many investigators<sup>8</sup> have reported that the LBB system consists of three major conduction pathways ('trifascicular system'). Lazzara and colleagues<sup>9</sup> studied the activation sequences of the left conducting tissue and septal myocardium before and after transection of the proximal LBB using rather large specimens isolated from the canine left ventricle. This study indicated the functioning of the septal Purkinje fibers as an independent pathway from the AF and PF in physiological conditions. Several experiments on *in vivo* canine hearts<sup>3</sup> suggested that the activation of the left ventricular muscle of the septum is initiated by propagated impulses predominantly through the septal Purkinje fibers. In addition an anatomical study<sup>10</sup> on the canine ventricular special conduction system showed the trifascicular system of the LBB system consisting of the anterior and posterior primary branches and a vast network of fibers extending between the major branches in the LBB system.

In the present study with the purpose of elucidating the mechanism of ventricular aberrant conduction with an RBB block pattern, both

- J Regional refractoriness within the ventricular conduction system *Circ Res* 39:254 1976
- 7 Iwamura N, Shimizu T., Kodama I, Toyama J and Yamada K. In vitro study on the cause of intraventricular aberrant conduction. Comparison of the functional refractory period between the canine right and left bundle branch systems *Jpn Circ J* 40:461 1976
- 8 Myerburg R J, Stewart J W. and Hoffman B F. Electrophysiological properties of the canine peripheral A-V conducting system *Circ Res* 26:361 1970
- 9 Myerburg F J, Gelband H. and Hoffman B F. Functional characteristics of the gating mechanism in the canine A-V conducting system *Circ Res* 28:136 1971
- 10 Uhley H N. and Rivkin L. Peripheral distribution of the canine A-V conduction system *Am J Cardiol* 25:688 1960
- 11 Hishida H. IRBBB pattern after incising a subdivision of the right bundle branch *Jpn Heart J* 10:300 1969
- 12 Durrer D, Van Dam R T, Freud G E, Janse M J, Meijler F S. and Arzbacher R C. Total excitation of the isolated human heart *Circulation* 41:899 1970
- 13 Schulenburg R M. and Durrer D. Rate-dependency of functional block in the human His bundle and bundle branch Purkinje system *Circulation* 48:526 1973
- 14 Massing R K. and James T N. Anatomical configuration of the His bundle and bundle branches in the human heart *Circulation* 53:609 1976
- 15 Cohen S I, Lau S H., Stein E., Young M W., and Damato A N. Variations of aberrant ventricular conduction in man. Evidence of isolated and combined block within the specialized conduction system *Circulation* 38:899 1968



transection of the lateral branches (false tendons) resulted in incomplete BRR block patterns. This study has suggested that the anterior septal or posterior branches of the RBB have much less functional significance as conduction pathways in physiological conditions compared with a dense distribution of lateral branches on the right ventricular free wall. In our experiments, consequently, we did not record action potentials from these smaller ramifications of the anterior septal or posterior branches though the APD and FRP were measured at the main RBB and its subsequent false tendons.

In the isolated human heart Durrer and co-workers<sup>1</sup> have elucidated three sites of the left ventricle at which the earliest muscle activation is observed suggesting the functioning of three major conduction pathways in the LBB system. Thus, if our results obtained from the canine heart can be to some degree extrapolated to the human heart, the higher incidence of aberrant conduction with an RBB block pattern in the majority of clinical electrocardiograms may be attributed to shorter refractory periods of the septal Purkinje fibers in the human heart also. Also, since differences in refractory periods<sup>12</sup> between the septal Purkinje fibers of the LBB system and the RBB tend to increase at slow heart rates, aberrant conduction of supraventricular premature beats following longer preceding periods is likely to result in complexes showing an RBB block configuration.

A recent anatomical study<sup>13</sup> on the specialized conduction system of the human heart has indicated the presence of the mid-septal Purkinje fibers and moreover, the extreme variability of these fiber groups especially in the proximal portion of the LBB. In agreement with this study, we observed a rather poorly developed distribution of the septal Purkinje fibers near the proximal LBB in some preparations. If the septal Purkinje network can not function effectively as a conduction pathway for premature impulses due to such variety of distribution of these fiber groups as mentioned above, various patterns of aberrancy in the QRS<sup>14</sup> may be brought on in addition to the typical configuration of RBB block in the human heart.

## Summary

To elucidate the mechanism underlying ventricular aberrant conduction, in each of 18 experiments we measured action potential durations

(APD) and functional refractory periods (FRP) of the Purkinje fiber along the following four conduction pathways in a pair of the right and left specimens isolated from the same canine heart: (1) the right bundle branch (RBB) and its subsequent false tendon, (2) the anterior fascicle (AF), (3) the posterior fascicle (PF), and (4) the septal Purkinje fiber of the left bundle branch (LBB) system. Both the APD and the FRP of the septal Purkinje fiber on the left septal surface were significantly shorter than those of the RBB, the AF, and PF of the LBB system, though we found no meaningful differences in the APD and the FRP among the false tendons of the RBB, the AF, and PF. It was thus suggested that the electrophysiological properties of the septal Purkinje fiber might have functional significance in premature activation of the LBB system. In order to verify this hypothesis furthermore we studied the sequential activation of the left conducting tissue and muscle cells of the left septal surface, applying a premature stimulus to the main LBB at a critical coupling interval which was nearly equal to the refractory periods of the AF and PF. The test impulse was propagated to the entire septal surface through the septal Purkinje fiber resulting in the initial muscle activation at almost the same area of the middle or lower third of the midseptum as in normal activation of the LBB system. The result indicates that the septal Purkinje network functions as the quickest pathway for conduction of premature impulses to the septal myocardium and suggests that the functional properties of this fiber group contribute to the higher incidence of RBB block in ventricular aberrant conduction of supraventricular premature beats.

## REFERENCES

1. Lazzara R, Yeh D K and Samet P. Functional anatomy of the canine left bundle branch. *Am J Cardiol* 33:623-1974.
2. Myerburg R J, Nilsson K and Gelband H. Physiology of canine intraventricular conduction and endocardial excitation. *Circ Res* 30:217-1972.
3. Venero E R, S. Seidenstein M, Stuckey J H and Hoffman B F. Activation of subendocardial Purkinje fibers and muscle fibers of the left septal surface before and after left bundle branch block. *Am Heart J* 83:346-1962.
4. Spach M S, Huang S and Ayers C R. Electrical and anatomical study of the Purkinje system of the canine heart. *Am Heart J* 65:664-1963.
5. Burch G E, Wajszczyk W J and Cronvich J A. Spread of activation in the anterolateral papillary muscle of the left ventricle of the dog under normal and pathologic conditions. *Am Heart J* 79:769-1970.
6. Lazzara R, El Sherif N, Befeler R and Scherlag H

## RADIOIMMUNOASSAY OF SERUM MYOGLOBIN

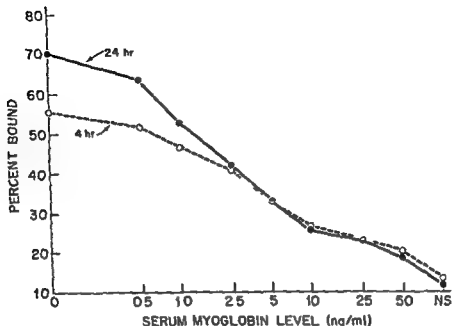


Fig 1 Standard curves utilizing the 4-hour (broken line) and 24 hour (solid line) radioimmunoassay determinations for serum myoglobin

and the serum sample to be tested the tubes were placed on a shaker in a cold room at 4° C for 4 hours. Separation of bound from free myoglobin was then accomplished utilizing 50 per cent ammonium sulfate to precipitate the bound myoglobin. Precipitates were subsequently counted as described previously.

Sera were obtained from patients complaining of chest pain who were seen in the Emergency Room at Parkland Memorial Hospital in Dallas, Texas, during July and August 1976 (Table I). Sera were also obtained from 14 patients with renal failure who were being treated at Parkland Memorial Hospital. Verbal informed consent was obtained for the venous blood collections. All patients' sera were stored at -20° C until they were assayed.

### Results

Typical standard curves utilizing both the 4 and 24 hour radioimmunoassay methods for determination of serum myoglobin were performed simultaneously with each set of patient samples that were analyzed (Fig 1). Five additional standard curves were run on different days utilizing both methods and the results obtained on each occasion were essentially identical. A

concentration of 0.5 ng per tube (2.5 ng/ml) was detected by both the 4- and 24-hour methods.

**Precision, reproducibility, specificity.** Each sample was run in triplicate and the results agreed within 3 per cent. Four determinations were run on different days on a sample of normal human sera with the coefficient of variation being 3 per cent for the 24-hour test and 18 per cent for the 4-hour test. In every instance if a patient's serum sample had a high myoglobin value, it was high in both the 4- and 24-hour assays. The specificity of the assay for myoglobin has previously been documented as has the lack of cross-reactivity with other plasma and intracellular proteins.<sup>1</sup> The data indicate that the 4-hour radioimmunoassay for determination of serum myoglobin is a specific and accurate test for measuring myoglobin levels.

All sera tested were found to have detectable myoglobin levels. In 53 individuals complaining of chest pain but without subsequent clinical evidence of acute myocardial infarcts, the average serum myoglobin value determined by 4-hour radioimmunoassay was 33.8 ng/ml (Fig 2). Only two patients evaluated in this group had serum myoglobin values above 85 ng/ml; one had unstable angina pectoris and had been drinking

# Detection of myoglobin by radioimmunoassay in human sera Its usefulness and limitations as an emergency room screening test for acute myocardial infarction

Gary Gilkeson, BS\*  
Marvin J Stone, MD  
Michael Waterman, PhD  
Ruby Ting MA  
Celso E Gomez Sanchez MD  
Alan Hull MD  
James T Willerson, MD, FACC\*\*  
Dallas Texas

We have previously described the development of a radioimmunoassay for the measurement of serum myoglobin values and have indicated that serum myoglobin determinations utilizing this method are of value in patients in detecting the presence of acute myocardial infarcts.<sup>1</sup> This determination previously required a 24 hour incubation time between labeled antigen and antibody prior to being able to determine serum myoglobin values.<sup>1</sup> The relatively long time period required for the determination of serum myoglobin values by radioimmunoassay precluded using the test as a possible screening test<sup>1</sup> for the presence of myocardial infarction in the Emergency Room. Therefore we have further

modified the assay so that determinations of serum myoglobin can be made within 4 hours. We have utilized this shorter radioimmunoassay to test whether serum myoglobin measurements might be used to detect the presence or absence of myocardial infarction in the Emergency Room in patients presenting with chest pain. In addition we have also utilized this radioimmunoassay to determine whether patients with marked renal insufficiency have abnormal elevations of serum myoglobin and whether there are additional patient groups seen in the Emergency Room setting that might also have elevated serum myoglobin values in the absence of acute myocardial infarction.

## Materials and methods

The method for the purification of myoglobin, immunization of rabbits and the radiolabeling of myoglobin is the same as we have described previously.<sup>1</sup> The radioimmunoassay procedure utilized in the present study is also similar, but differs from our previously described method in the following ways. In the present shortened version of the radioimmunoassay for serum myoglobin all assays were performed in triplicate in 12 x 75 mm glass tubes which were siliconized in a 1:100 silicone solution. After the addition of the <sup>125</sup>I myoglobin, the anti myoglobin antibody,

From the Departments of Internal Medicine and Biochemistry at Southwestern Medical School, The University of Texas Health Science Center at Dallas, Dallas, Texas.

This study was supported by National Institutes of Health Ischemic Heart Disease Specialized Center of Research (SCOR) Grant HL 17669, National Institutes of Health Grant HL 1572 and by the American Heart Association Grant 75-819.

Received for publication Mar 18 1977

Accepted for publication April 19 1977

Reprint requests James T Willerson MD, Ischemic Heart Center L5 134, University of Texas Health Science Center, 323 Harry Hines Blvd, Dallas, Texas 75235.

Mr. Gilkeson is presently a sophomore medical student at Southwestern Medical School.

Dr. Willerson is an Established Investigator of the American Heart Association.

any other evidence of having had an acute myocardial infarct. Three patients were seen in the Emergency Room with chest pain resulting from pericarditis; the serum myoglobin level was normal in all three. Four patients were evaluated in the Emergency Room with congestive heart failure and nonspecific chest pain; each of these patients had a normal serum myoglobin value. Three patients were evaluated with recent onset of atrial fibrillation; each of these patients had a normal serum myoglobin determination. Two patients were evaluated with diabetic acidosis: one with drug overdose and one with galvanic inhalation; these patients did not have clinical evidence of acute myocardial infarcts and their serum myoglobin levels were also normal. Finally, two patients with pancreatitis and two in shock without evidence of acute myocardial infarcts were also seen. Both patients with pancreatitis had normal serum myoglobin values. The two patients with shock and absent systolic pressures both had elevated serum myoglobin values initially (1,750 and 500 ng/ml respectively); in these patients the circulatory collapse was due to systemic sepsis and the patient with the highest serum myoglobin value died while the other one survived.

A total of 13 blood samples were obtained from patients seen in the Emergency Room who were subsequently diagnosed as having suffered an acute myocardial infarction (Table I). The determination of myocardial infarction was made on the basis of the following: (1) a typical history of prolonged and severe chest pain ordinarily associated with diaphoresis and nausea; (2) classical ECG changes including the development of significant Q waves for acute transmural myocardial infarctions or ST-T wave abnormalities consistent with the diagnosis of acute non-transmural (subendocardial) myocardial infarction; (3) classical evolution of serum creatine kinase values; and (4) the development of a positive technetium 99m stannous pyrophosphate myocardial scintigram. Five of these 13 patients had increased serum myoglobin values when initially seen in the Emergency Room (Table I). The mean serum myoglobin level in these five patients was 739 ng/ml with a range from 105 to 2,900 ng/ml (Fig. 2). A second serum sample was obtained during the first 6 to 8 hours following admission in five of the remaining patients and in four it was elevated.

The mean serum myoglobin level 6 to 8 hours following hospital admission in these four patients was 401 ng/ml; this represented a rise from the mean serum value of 335 ng/ml obtained in the Emergency Room in these same patients. Two of the patients with high second serum myoglobin levels had another more prolonged episode of chest pain following admission to the hospital, suggesting that they may have suffered their myocardial infarcts after admission to the hospital. In the remaining four patients without elevated serum myoglobin levels in the Emergency Room, two were subsequently discovered to have entered the hospital more than 24 hours after the onset of symptoms suggestive of myocardial infarction and were thus seen too late for the serum myoglobin levels to be elevated. One of the remaining two patients with acute myocardial infarcts did not have a second serum sample obtained for analysis; in the final patient two serum samples were obtained for serum myoglobin analysis but both values were normal.

Two additional patients with recent myocardial infarcts (one 3 and one 10 days earlier) were evaluated because of recurrent chest pain. In both of these patients no definite evidence of infarct extension was found and serum myoglobin values were normal in both. Three patients were cardioverted for supraventricular tachyarrhythmias following admission to the hospital; in each of these patients sera for myoglobin determinations were obtained 6 to 8 hours and 22 to 30 hours after cardioversion. In each of these patients the serum myoglobin was normal; none of the three subsequently developed evidence of having had acute myocardial infarcts (Table I).

Sera were also obtained for myoglobin measurements in 14 patients with severe renal disease (Fig. 2, Table I). In those patients being dialyzed, the serum samples for myoglobin and creatinine determinations were obtained immediately prior to dialysis. Elevated serum myoglobin values were found in all patients with serum creatinine values above 8 mg per cent.

#### Discussion

The data from this study demonstrate that serum myoglobin may be determined by radioimmunoassay with a 4 hour test. The results obtained with the 4 hour shortened method are

# SERUM MYOGLOBIN VALUES AS DETERMINED BY 4 HOUR RADIOIMMUNOASSAY IN EMERGENCY ROOM EVALUATION

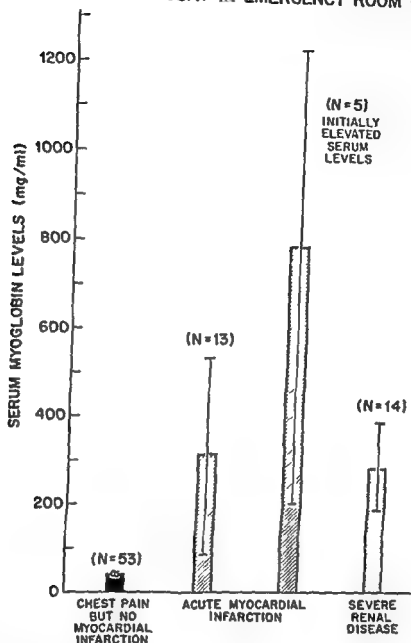


Fig 2 Serum myoglobin values in the patients evaluated in this series. Bars represent mean values and the cross bars connected by vertical lines represent the standard errors.

heavily (J G see below) and the other one (U A) who was subsequently sent home had chest pain which on clinical grounds was felt not to be due to myocardial infarction (Table I). Therefore as with the 24 hour radioimmunoassay for serum myoglobin determination any value over 85 ng/ml was considered abnormal. In this group of patients 10 were admitted to the coronary care unit to rule out an acute myocardial infarct and were subsequently found not to have had one. Each of these ten patients had a normal serum myoglobin value in the Emergency Room determination. Twelve patients were discharged

from the Emergency Room as having chest pain that did not suggest any definite significant medical illness in each of these patients the serum myoglobin level was normal in the Emergency Room. Thirteen additional patients were admitted to the hospital with a diagnosis of unstable angina pectoris, in 12 the serum myoglobin level was normal in the Emergency Room. One patient in this group had an elevated serum myoglobin value. This patient had been consuming large amounts of alcohol prior to admission (serum myoglobin value 180 ng/ml). None of these patients subsequently developed

Table I Cont'd

| Patient<br>no &<br>initials | Age | Diagnosis                   | Serum<br>myoglobin<br>level<br>(ng/ml) |  |
|-----------------------------|-----|-----------------------------|--|--|
|                             |     |                             | Emerg<br>ency<br>Room                  | Mg globin<br>deter-<br>mined<br>6-8 hours<br>later |
| 40 B B                      | 37  | Mitral prolapse             | 70                                     |  |
| 41 K C                      | 67  | Atrial fibrillation         | 42                                     |  |
| 42 J W                      | 81  | Atrial fibrillation         | 15                                     |  |
| 43 J D                      | 27  | Atrial fibrillation         | 49                                     |  |
| 44 G H                      | 49  | Pericarditis                | 70                                     |  |
| 45 J M                      | 53  | Pericarditis                | 41                                     |  |
| 46 E H                      | 61  | Pericarditis                | 70                                     |  |
| 47 J H                      | 67  | Congestive heart<br>failure | 40                                     |  |
| 48 A B                      | 64  | Congestive heart<br>failure | 3                                      |  |
| 49 J L                      | 8   | Congestive heart<br>failure | 23                                     |  |
| 50 S W                      | 80  | Congestive heart<br>failure | 17                                     |  |
| 51 L W                      | 28  | Diabetes                    | 21                                     |  |
| 52 C Y                      | 79  | Diabetes                    | 25                                     |  |
| 53 O L                      | 43  | Drug overdose               |  |  |

## III Patients in shock but without myocardial infarction

|       |    |       |     |
|-------|----|-------|-----|
| 1 J B | 73 | Shock | 500 |
| 2 C V | 31 | Shock | 150 |

## IV Patients electrically cardioverted

|       |    |                                 |     |
|-------|----|---------------------------------|-----|
| 1 L A | 64 | Supraventricular<br>tachycardia | 175 |
| 2 R H | 51 | Supraventricular<br>tachycardia | 10  |
| 3 S C | 40 | Supraventricular<br>tachycardia | 60  |

## V Patients with renal disease

| Patient | Serum<br>creatinine<br>(mg %) | Serum<br>myoglobin<br>level (ng/ml) |
|---------|-------------------------------|-------------------------------------|
| 1 C M   | 18.8                          | 250                                 |
| 2 G W   | 1                             | 175                                 |
| 3 J R   | 9.6                           | 460                                 |
| 4 L A   | 2.2                           | 1                                   |
| 5 L B   | 1                             | 70                                  |
| 6 G A   | 8.8                           | 270                                 |
| 7 L H   | 10.3                          | 370                                 |
| 8 F T   | 12                            | 90                                  |
| 9 P T   | 10                            | 8                                   |
| 10 F G  | 16                            | 1400                                |
| 11 J J  | 39                            | 220                                 |
| 12 J J  | 12.3                          | 12                                  |
| 13 J P  | 3.6                           | 3                                   |
| 14 S A  | 12.1                          | 9                                   |

similar to those found with the 24 hour incubation period we have previously described.<sup>1</sup> Thus this reduction in time required to perform the test should allow more rapid determinations of serum myoglobin by radioimmunoassay and make evaluations potentially more useful in the clinical setting.

Our attempts to utilize the shortened radioimmunoassay determination of serum myoglobin as a triage test for patients seen in the Emergency Room with chest pain immediately after hospital admission were only partially successful. Approximately 40 per cent of patients admitted to the hospital with severe chest pain who subsequently did have acute myocardial infarcts documented by serial enzyme and ECG testing and <sup>99m</sup>Tc PYP myocardial scintigraphy had elevated serum myoglobin levels in the Emergency Room. In contrast another 30 per cent developed elevated serum myoglobin levels at the time of the second determinations which were within 6 to 8 hours following being seen in the Emergency Room. In two of these patients it appeared that the actual acute myocardial infarct might have occurred following admission to the hospital since both of these patients had additional even more prolonged episodes of chest pain associated with nausea and sweating following being admitted to the hospital. Two of the remaining four patients that did not elevate their serum myoglobin levels had their acute myocardial infarcts 24 or more hours prior to coming to the Emergency Room and in the final two patients serum myoglobin elevations did not develop even though acute myocardial infarcts were documented. In one only the initial Emergency Room serum myoglobin value was obtained for testing but in the other both an Emergency Room and a second sample were available. Presumably in the latter patient the extent of myocardial damage was small enough that serum myoglobin elevation did not occur. Thus there are definite temporal and probably quantitative limitations in the utilization of serum myoglobin determinations for establishing the diagnosis of acute myocardial infarction. If the patient presents to the hospital less than 2 or more than 24 hours after his acute myocardial infarct then it will often be difficult to establish the presence of the infarct with a single serum myoglobin determination.<sup>1,2</sup> Moreover if the myocardial infarct is quantitatively a

Table 1 Serum myoglobin values in patients studied

| Patient no & initials                              | Age | Diagnosis   | Serum myoglobin level (ng /ml) |                                      |
|--|-----|-------------|--------------------------------|--------------------------------------|
|  |     |             | Emergency Room                 | Myoglobin determined 6-8 hours later |
| <i>I Patients with acute myocardial infarction</i> |     |             |                                |                                      |
| 1 E V  | 62  | SEMI*       | 105                            | ND                                   |
| 2 P B  | 70  | Inf MI*     | 2900                           | ND                                   |
| 3 M B  | 60  | Inf lat MI* | 35                             | ND                                   |
| 4 E M  | 61  | Inf MI      | 175                            | ND                                   |
| 5 R B  | 59  | Inf MI      | 15                             | 320                                  |
| 6 D H  | 76  | Ant MI*     | 60                             | 600                                  |
| 7 N C  | 51  | Inf MI      | 400                            | ND                                   |
| 8 J G  | 44  | Lat MI      | 33                             | 205                                  |
| 9 D D  | 45  | SEMI        | 130                            | ND                                   |
| 10 C R   | 60  | Inf MI      | 160                            | ND                                   |
| 11 A A   | 58  | Inf MI      | 45                             | 50                                   |
| 12 J W   | 64  | Inf lat MI  | 26                             | 480                                  |
| 13 M A   | 68  | Inf lat MI  | 47                             | ND                                   |

*II Patients with chest pain but no clinical evidence of myocardial infarct*

|        |    |                          |     |  |
|--------|----|--------------------------|-----|--|
| 1 G D  | 50 | Unstable angina pectoris | 25  |  |
| 2 T P  | 44 | Unstable angina pectoris | 65  |  |
| 3 A T  | 68 | Unstable angina pectoris | 60  |  |
| 4 J M  | 77 | Unstable angina pectoris | 41  |  |
| 5 I F  | 61 | Unstable angina pectoris | 31  |  |
| 6 M W  | 50 | Unstable angina pectoris | 31  |  |
| 7 B J  | 71 | Unstable angina pectoris | 43  |  |
| 8 W B  | 53 | Unstable angina pectoris | 38  |  |
| 9 E M  | 46 | Unstable angina pectoris | 28  |  |
| 10 J G | 53 | Unstable angina pectoris | 180 |  |
| 11 J O | 47 | Unstable angina pectoris | 22  |  |
| 12 E O | 45 | Unstable angina pectoris | 36  |  |
| 13 B F | 48 | Unstable angina pectoris | 4   |  |

Abbreviations ND = not obtained SEMI = acute subendocardial myocardial infarct Inf MI = acute inferior myocardial infarct Inf lat MI = acute inferolateral myocardial infarct Ant MI = acute anterior myocardial infarct

Table 1 Cont'd

| Patient no & initials | Age | Diagnosis                                  | Serum myoglobin level (ng/ml) |                                      |
|-----------------------|-----|--|-------------------------------|--------------------------------------|
|                       |     |  | Emergency Room                | Myoglobin determined 6-8 hours later |
| 14 H W                | 54  | Chest pain of uncertain etiology but no MI | 25                            |                                      |
| 15 L C                | 65  | Chest pain of uncertain etiology but no MI | 26                            |                                      |
| 16 J E                | 61  | Chest pain of uncertain etiology but no MI | 29                            |                                      |
| 17 D K                | 42  | Chest pain of uncertain etiology but no MI | 28                            |                                      |
| 18 T A                | 49  | Chest pain                                 | 175                           |                                      |
| 19 B C                | 79  | Chest pain                                 | 20                            |                                      |
| 20 A G                | 52  | 10 day old MI                              | 29                            |                                      |
| 21 L C                | 56  | 3 day old MI                               | 31                            |                                      |
| 22 J H                | 47  | Insignificant chest pain                   | 59                            |                                      |
| 23 C W                | 60  | Insignificant chest pain                   | 15                            |                                      |
| 24 L M                | 35  | Insignificant chest pain                   | 18                            |                                      |
| 25 G M                | 49  | Insignificant chest pain                   | 45                            |                                      |
| 26 P S                | 65  | Insignificant chest pain                   | 22                            |                                      |
| 27 R G                | 65  | Insignificant chest pain                   | 32                            |                                      |
| 28 C S                | 73  | Insignificant chest pain                   | 25                            |                                      |
| 29 M B                | 58  | Insignificant chest pain                   | 23                            |                                      |
| 30 J E                | 55  | Insignificant chest pain                   | 55                            |                                      |
| 31 W R                | 53  | Insignificant chest pain                   | 35                            |                                      |
| 32 U A                | 60  | Insignificant chest pain                   | 100                           |                                      |
| 33 R F                | 64  | Insignificant chest pain                   | 28                            |                                      |
| 34 J M                | 47  | Insignificant chest pain                   | 35                            |                                      |
| 35 V D                | 21  | Pleurisy                                   | 33                            |                                      |
| 36 E B                | 64  | Pleurisy                                   | 75                            |                                      |
| 37 H R                | 41  | Pancreatitis                               | 75                            |                                      |
| 38 M J                | 58  | Pancreatitis                               | 20                            |                                      |
| 39 W B                | 48  | Galvanic inhalation                        | 35                            |                                      |

- Results in patients with acute myocardial infarction *J Clin Invest* 56 1334 1975
2. Stone M J., Waterman M R Murray G et al The serum myoglobin level as a diagnostic test in patients with acute myocardial infarction *Br Heart J* 38 375 1977
3. Willerson J T Polner L Buja L M et al Myoglobinemia as a clue to the presence of acute myocardial infarction (Abstr) *Clin Res* 24 427A 1976
4. Kagen L J Clinical considerations in Myoglobin Biochemical physiological and clinical aspects New York and London 1973 Columbia University Press Chapt. 6, pp 79 116.
5. Koskela P Kekki M and Wager H Kinetic behavior of  $^{51}\text{I}$  labelled myoglobin in human beings *Clin. Chim Acta* 17 339 1967
6. Willerson J T., Parkey R W Bonte F J et al Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology *Circulation* 51 1046 1975
7. Donsky M S Curry H C Parkey R W et al Unstable angina pectoris Clinical, angiographic and myocardial scintigraphic observations *Br Heart J* 38 257 1976



small one, serum myoglobin levels may not rise. We have previously established in awake, unanesthetized experimental animals with myocardial infarcts that serum myoglobin levels begin to rise within 2 hours after left anterior descending coronary artery occlusion and generally return to normal within 24 hours after experimental infarction.<sup>1</sup> In these same studies experimental myocardial infarcts as small as 3 gms were associated with increased serum myoglobin values and the general extent of the infarct histologically was strongly correlated with peak serum myoglobin levels.<sup>1</sup> The present results stress the difficulty in dating the onset of acute myocardial infarction in patients and this, of course, represents a definite limitation in the utilization of the rapid determination of serum myoglobin in the recognition of acute myocardial infarcts.

It also appears that shock, irrespective of its etiology, and severe renal insufficiency and in particular renal insufficiency associated with serum creatinine levels equal to or greater than 8 mg per cent are associated with elevated serum myoglobin levels. In the case of circulatory collapse and shock, presumably anoxia with subsequent skeletal muscle damage is responsible for elevated serum myoglobin levels. Shock is of course, known to increase certain serum enzyme values which are routinely used in the evaluation of patients for possible myocardial infarction. In addition, we found one patient with none of these abnormalities who had been drinking heavily for several days prior to being seen in the Emergency Room who also had elevated serum myoglobin and creatine kinase levels. Thus it may be that alcohol itself in excess is capable of producing serum myoglobin elevations as a consequence of skeletal muscle damage. While we cannot prove that alcohol in excess was responsible for the serum myoglobin elevation in this patient, we feel that other investigators should be aware of this possibility so that the potential association can be further tested as other patients are evaluated. Elevated serum myoglobin values in patients with severe renal disease could be the result of either decreased excretion and/or impaired metabolism of serum myoglobin as a result of the severe renal insufficiency.<sup>4,5</sup>

We did not find elevated serum myoglobin levels in the majority of patients with unstable angina pectoris but without enzymatic or electrocardiographic evidence of myocardial necrosis.

We have previously indicated that one third of patients with unstable angina pectoris have positive technetium 99m stannous pyrophosphate myocardial scintigrams and this raises the question as to whether or not these patients have had limited myocardial necrosis not detected by routine enzymatic and electrocardiographic testing.<sup>6,7</sup> The answer to this question is difficult to provide since temporal considerations are important, i.e., the majority of these patients have had chest pain in a crescendo pattern for several days and sometimes for several weeks, thus dating the time of possible myocardial necrosis is at best difficult. In the present series of 13 patients with unstable angina pectoris 11 had technetium 99m stannous pyrophosphate myocardial scintigrams and in each instance they were negative. In the remaining two patients no myocardial scintigrams were obtained.

### Summary

The results indicate that serum myoglobin determinations may be obtained by radioimmunoassay utilizing time periods for the testing which allow more useful clinical evaluation of patients. The data also demonstrate, however, that there are important temporal considerations in using serum myoglobin levels for the detection of acute myocardial infarcts and if this test is used to determine in the Emergency Room whether patients have had acute myocardial infarcts these limitations will have to be kept in mind. In addition three other patient subgroups that might be expected to have elevated serum myoglobin levels by radioimmunoassay have been determined. These include patients with shock (irrespective of etiology), patients with severe renal insufficiency, i.e., those with serum creatinine levels equal to or greater than 8 mg per cent, and possibly patients who have been on alcohol binges immediately prior to being seen in the Emergency Room.

The authors wish to express their appreciation to the medical house officers and nurses working in the Emergency Room at Parkland Memorial Hospital in Dallas, Texas without whose help these studies would not have been possible. Our appreciation is also expressed to Mrs. Belinda Lambert, Mrs. Donna Place and Mrs. Mary Rich for secretarial assistance.

### REFERENCES

1. Stone M J, Wallerson J T, Gomez Sanchez C E et al. Radioimmunoassay of myoglobin in human sera.

## Results

The effect of saralasin infusion upon mean arterial pressure heart rate and plasma catecholamine concentrations is shown in Table I. After five minutes of infusion mean arterial pressure rose significantly. Heart rate fell slightly but the change was not statistically significant. At the end of the 30 minute saralasin infusion the mean arterial pressure was not significantly different from control for the entire group. Mean arterial pressure rose 5 to 13 mm Hg in four patients remained unchanged in one and fell 9 mm Hg in one (a patient with renal artery stenosis). Neither plasma noradrenaline nor plasma adrenaline was significantly different from pre infusion levels at the end of the saralasin infusion.

Table II demonstrates the effect of noradrenaline infusion. Mean arterial pressure rose significantly and to a degree comparable to the change observed during the first five minutes of saralasin infusion. Heart rate fell significantly. However the change in heart rate produced by noradrenaline infusion was not significantly different from that observed during the first five minutes of saralasin infusion. The large increase in plasma noradrenaline concentration observed during noradrenaline infusion was 13 times that observed during the first five minutes of saralasin administration. A small but significant increase in plasma adrenaline concentration was observed during noradrenaline infusion.

## Discussion

Several of the angiotensins and structurally related peptides including those with antagonist action produced by substitution of alanine for phenylalanine in the 8 or C terminal position have been shown to release catecholamines from the adrenal medulla. If this release were to have any physiologic action in man it might be expected that an increase in arterial pressure would be accompanied by an increase in heart rate since adrenaline is the predominant catecholamine of human adrenal medulla. The effect of saralasin infusion during the first five minutes of administration was to cause an increase in arterial pressure without any significant change in cardiac rate. The alterations in plasma catecholamine concentration at this point were limited to a small but significant increase in plasma noradrenaline concentration without an appreciable change in adrenaline. More prolonged

**Table I** Effect of saralasin upon mean arterial pressure (MAP) heart rate (HR) plasma noradrenaline (NA) and adrenaline (A) concentration after 5 and 30 minutes of infusion

|                   | Control  | 5 Minutes | 30 Minutes |
|-------------------|----------|-----------|------------|
| MAP (mm Hg)       | 121 ± 3  | +13 ± 4   | +4 ± 3     |
| HR (beats/min)    | 73 ± 6   | -4 ± 2    | -2 ± 1     |
| Plasma NA (pg/mL) | 245 ± 34 | +115 ± 28 | +30 ± 23   |
| Plasma A (pg/mL)  | 48 ± 5   | +5 ± 2    | +6 ± 4     |

All results are expressed as mean ± SEM. Values at 5 and 30 minutes are the change from control level.

P < 0.025

P < 0.01.

**Table II** Effect of noradrenaline infusion upon MAP HR plasma NA and A concentrations

|                   | Control  | Infusion     |
|-------------------|----------|--------------|
| MAP (mm Hg)       | 117 ± 3  | +10 ± 3      |
| HR (beats/min)    | 76 ± 3   | -7 ± 1       |
| Plasma NA (pg/mL) | 347 ± 37 | +1,567 ± 160 |
| Plasma A (pg/mL)  | 39 ± 5   | +13 ± 3      |

Results are expressed in Table I

P < 0.01

infusion of saralasin was no longer associated with any significant change in concentration of either plasma catecholamine.

Since the hemodynamic changes observed during the first few minutes of saralasin infusion resembled that which might be due to alpha adrenergic stimulation noradrenaline was infused at a rate which gave an increase in mean arterial pressure similar to that which was produced by saralasin at five minutes. Despite the similarity in change of arterial pressure plasma noradrenaline rose to a much greater extent than was observed during saralasin infusion. Thus although the hemodynamic changes associated with the transient pressor response to saralasin bear some similarity to what might be expected from an alpha receptor antagonist the amount of circulating noradrenaline measured during saralasin infusion fails to account for the observed change in pressure when compared to infusion of noradrenaline. The small increase in plasma noradrenaline detected during the initial pressure response to saralasin while having no hemody-

# Effect of saralasin upon plasma catecholamines in hypertensive patients

Nicolas D Vlachakis, M D

Artur B Ribeiro, M D

Lawrence R Krakoff, M D

New York N Y

Saralasin, (sarcosine 1, alanine 8, angiotensin II) a peptide antagonist of the vascular action of angiotensin II, reduces arterial pressure in subjects with high levels of circulating renin.<sup>1</sup> However during the first few minutes of administration of saralasin, a pressor response is often observed regardless of the effect of more prolonged action of the drug.<sup>2-4</sup> The transient pressor action of saralasin might be explained by the hormones of the adrenal medulla for it has been demonstrated that angiotensin and other peptides release epinephrine and norepinephrine from this organ.<sup>5</sup> Also, it has recently been reported that a hypertensive crisis occurred during infusion of saralasin in a patient with pheochromocytoma.<sup>6</sup> In order to assess the significance of catecholamines from the adrenal medulla in the transient pressor action of saralasin the effect of this peptide upon hemodynamics and plasma catecholamine concentration was compared to the effect of catecholamine infusion.

## Methods

Saralasin infusion studies were carried out in six patients. Noradrenaline infusions were performed in seven patients. Pheochromocytoma was excluded by determination of urine meta-

nephrine excretion in all subjects prior to any infusion studies. Infusion studies were performed during hospitalization while patients were ingesting diets containing 80 to 100 mEq sodium. Diuretics were not administered. Infusion studies were carried out in the supine position. At one minute intervals blood pressure was measured by the Roche Arteriosonde 1216 and cardiac rate was monitored by electrocardiogram. Saralasin was given intravenously at a dose of 10 µg/kg/minute for a 30 minute period. Blood samples for plasma noradrenaline and adrenaline were taken from an indwelling catheter prior to infusion after five minutes (just after the peak of the pressor response) and at the end of the infusion. Noradrenaline was given at a rate of 0.1 µg/Kg/minute for 15 minutes and blood samples were obtained just before and at the end of the infusion. Blood pressure measurements represent the difference between the means of 10 control determinations prior to infusion and of three determinations bracketing the time reported (i.e., for five minutes the mean of blood pressure taken at 4, 5 and 6 minutes).

Plasma catecholamine concentrations were determined by a sensitive and specific radioassay.<sup>7</sup> Forty to 100 µl aliquots of plasma in which catecholamines are preserved by the use of EDTA and glutathione are incubated with <sup>3</sup>H methyl S-adenosyl methionine and catechol O-methyltransferase to form metanephrine and normetanephrine. These amines are separated by thin layer chromatography and converted to vanillin by periodate oxidation. Interassay variation is less than 10 per cent and the absolute sensitivity is 1.0 picogram for either adrenaline or noradrenaline.

From the Hypertension Division, Department of Medicine, Mount Sinai School of Medicine of the City University of New York.

Supported by United States Public Health Service Grant HL 13595

and by Clinical Center Grant RR 71.

Received for publication May 3 1977.

Accepted for publication June 16 1977.

Reprint requests: Lawrence R. Krakoff, M.D., Associate Professor of Medicine, Chief Hypertension Division, Mount Sinai School of Medicine, Fifth Avenue and 100th St., New York, N.Y. 10079.

## Case reports

### Relationship between myocardial infarction and preinfarction angina\*

A histopathological study of coronary arteries in two sudden death cases employing serial section

Toshinobu Horie M D  
Morie Sekiguchi M D  
Kosichiro Hirokawa M D  
Tokyo Japan

It is necessary to clarify the initiating causes of acute myocardial infarction in order to treat or prevent this disease.

So far we have studied 108 autopsied cases of acute myocardial infarction and have obtained the following results:

1 Serial section of the coronary artery is needed because pathology of the lumen is extremely variable within any given 2 to 3 mm segment.

2 A high incidence of thrombus formation (80.3 per cent) was observed in cases where death occurred at the acute stage.

3 Occluding coronary thrombi were usually formed at the proximal part of the coronary arteries and at the sites of ruptured atheromatous plaques (incidence rate 90.8 per cent).

4 The increase of intra plaque pressure resulting from a honeycomb like accumulation of foam cells, cholesterol clefts and blood infiltration from the lumen into the plaque through the injured endothelial barrier is we feel the cause of the rupture of the atheromatous plaque.

5 This fracture between the lumen and the

plaque might precede and be responsible for the formation of the thrombus and the onset of acute myocardial infarction.

6 Fresh occluding thrombi had already been formed in patients who died within 5 to 6 hours after the onset of acute myocardial infarction.

We thought it necessary to examine the patients who died suddenly after the attack of acute myocardial infarction in order to find the initiating causes of the disease.

Examining coronary arteries histologically by employing serial section we have investigated the relationship between the initiation of acute myocardial infarction and preinfarction angina.

#### Case reports

**Case 1** A 70-year old retired office worker was admitted with a 5 day history of chest pain. He had first noticed left precordial distress when climbing stairs and playing golf four years prior to the present illness. It promptly subsided with rest but appeared occasionally during effort. Thus he required no nitroglycerin. However four months before admission he discontinued playing golf due to the occurrence of constant pain during this exercise. Five days before admission he had a severe attack of precordial pain early in the morning which lasted for 10 minutes and which was relieved by one dose of nitroglycerin.

Unfortunately the pain returned gradually and increased daily in severity and duration. On the day of admission while resting in bed he suddenly developed a similar but more severe attack that lasted 1 minute. The pain was partially relieved just after 2 doses of nitroglycerin and on arrival at the CCL it had cleared completely.

**Physical examination** The patient was well developed and nourished and had no discomfort. The results of the examination were almost normal except for the presence of hypertension. Blood pressure was 180/100 mm Hg and heart rate was 70 beats per minute.

dynamic significance *per se*, may indicate a trivial release from the adrenal medulla or an alteration in function of sympathetic neurons. Neuronal reuptake of noradrenaline plays an important role in terminating the action of the sympathetic neuro transmitter,<sup>9</sup> suggesting that changes in plasma catecholamines will reflect sympathetic neuronal activity to a very limited extent.

The transient pressor effect of saralasin must be distinguished from the more prolonged elevation of arterial pressure that is observed when this drug is given to some hypertensive patients with low levels of circulating renin. The latter action of the peptide appears best related to a partial agonist function at the site of angiotensin II vascular receptors.<sup>10</sup> While the observations presented in this study tend to exclude release of adrenal medullary catecholamines as a cause of the transient pressor action of saralasin, they do not eliminate the possibility that changes in neuro secretion by adrenergic neurons may account for this phenomenon.

### Summary

The effect of saralasin, a clinically employed angiotensin antagonist upon hemodynamics and plasma catecholamine concentration was compared to the infusion of noradrenaline. These studies were carried out to determine if a transient pressor effect frequently observed during saralasin infusion might be mediated by release of catecholamines from the adrenal medulla. After five minutes of saralasin infusion, mean arterial pressure rose significantly, pulse rate fell slightly, and plasma noradrenaline increased by  $115 \pm 28$  pg/ml. Plasma adrenaline was unchanged. After 30 minutes of saralasin infusion, mean arterial pressure was at control levels and plasma catecholamine concentrations were also no different from pre infusion levels. Infusion of noradren-

aline produced a hemodynamic pattern similar to that observed during the first five minutes of saralasin infusion. However, there was a thirteen fold increase of plasma noradrenaline observed when compared to the first five minutes of saralasin infusion. It was concluded that the transient pressor action of saralasin could not be explained by release of catecholamines from the adrenal medulla. However, the very slight increase in plasma norepinephrine observed during the first five minutes of saralasin infusion may imply altered function of sympathetic neurons.

We express our thanks to the Norwich Pharmacal Company, Norwich, N.Y. for providing supplies of saralasin during this study.

### REFERENCES

1. Brunner H, Gavran H, Laragh J H and Keenan K. Hypertension in man. Exposure of the renin and sodium components using angiotensin II blockade. *Circ Res* 34 (Suppl 1) 35 1974.
2. Streeten D H P, Anderson G H, Freiberg J M and Dalakas T G. Use of an angiotensin II antagonist (saralasin) in the recognition of angiotensinogenetic hypertension. *N Engl J Med* 292 657 1975.
3. Marks L, Maxwell M H and Kaufman J J. Saralasin bolus test. *Lancet* II 784 1975.
4. Ribeiro A B and Krakoff L R. Angiotensin blockade in coarctation of the aorta. *N Engl J Med* 295 142 1976.
5. Peach M J. Adrenal medullary stimulation induced by angiotensin I, angiotensin II and analogues. *Circ Res* 28 and 29 (Suppl II) 107 1971.
6. Dunn F G, DeCarvalho J G R, Kem D C, Higgins J R and Frolich E D. Pheochromocytoma crisis induced by saralasin. *N Engl J Med* 295 605 1976.
7. Passon P G and Peuler J D. A simplified radiometric assay for plasma norepinephrine and epinephrine. *Anal Biochem* 51 618 1973.
8. Williams R H. Ed. Textbook of endocrinology. Philadelphia Pa. 1974. W B Saunders Company p 309.
9. Axelrod J and Weinschbaum R. Catecholamines. *N Engl J Med* 287 237 1972.
10. Hollenberg N K, Williams R H, Burger B, Ishikawa I and Adams D F. Blockade and stimulation of renal, adrenal and vascular angiotensin II receptors with 1 sar 8 ala angiotensin II in normal man. *J Clin Invest* 57 39 1976.

In cases where a thrombus was not detected coronary segments which showed the most severe stenosis were carefully examined by serial section. All sections were stained with hematoxylin-eosin Masson's trichrome Elastica van Gieson periodic acid methenamine silver (PAM) and phosphotungstic acid hematoxylin (PTAH)

Fig 5A a section of the right coronary artery 1.2 cm from the ostium shows an almost completely occluded coronary artery except for pinhole like canalization which is thought to be an old thrombus Figure 5B is a section from the left circumflex coronary artery at the branching site Here severe luminal stenosis is due to layered fibrous deposition probably formed during the frequent attacks

Fig 6A shows a section from the left anterior descending coronary artery 1.5 cm from the ostium Severe luminal stenosis is mainly attributed to atheromatous deposition Fig 6B under a higher magnification of 6A clearly shows the thinned intimal collagen fiber and infiltration of blood elements from the lumen into the atheromatous plaque through the endothelial barrier A careful microscopic examination revealed no special changes in this arterial section which could have caused sudden death Thus further sections around the site showing the most severe stenosis were made at intervals of 100 $\mu$

Fig 6C shows a section 500 $\mu$  more distal than Fig 6B In this picture rupture of the intimal collagen fiber is found The length of the fracture was 1800 $\mu$ , and the width was 800 $\mu$ . Discharge of the contents of the atheromatous plaque that is cholesterol clefts foam cells and ruptured intimal collagen fiber is also observed The ruptured ends of the intimal collagen fiber point toward the lumen at the fractured site These findings support the belief that the fracture occurs as a result of increasing intra plaque pressure Fibrin has already formed and surrounds the fractured intimal collagen fiber foam cells and cholesterol clefts so the appearance of fractured intimal collagen is not due to postmortem changes

Fig 6D shows a section 100 $\mu$  distal to that of Fig 6C The ruptured atheromatous plaque and the formation of fibrin is more clearly seen Fibrin and platelet aggregates adhere so strongly to the intimal collagen fiber facing the atheromatous plaque that they seem unremovable Here the intimal collagen fiber is rough and irregular so blood cells and platelets which have entered into the atheromatous plaque from the lumen are easily broken and thus platelet aggregates and fibrin are also produced

**Case 2** A 60-year-old retired office worker entered the hospital with an 11 hour history of chest pain Four years prior to his present illness he experienced a severe pain in the left anterior chest admitted and diagnosed as acute anteroseptal myocardial infarction Three years after discharge he was readmitted with angina pectoris Thereafter the pain gradually increased in severity and duration and required the administration of nitroglycerin

Ten hours before entry to the hospital he had a severe pain after dinner which subsided after two doses of nitroglycerin However as chest pain reoccurred every two hours and increased in intensity he was brought to our CCU by ambulance

**Physical examination** Blood pressure was 140/80 mm Hg heart rate was 100 beats per minute and temperature was 36.8°C

**Laboratory findings** White blood count was 10,000/mm



Fig 3 A through C A Electrocardiogram (made at 9:00 A.M.) on the monitor shows ST segment depression B ECG (made at 9:30 A.M.) during attack reveals ST segment elevation C Ventricular fibrillation

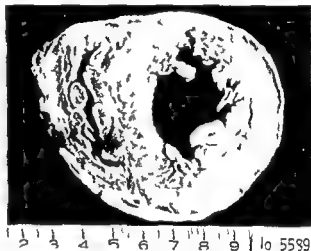
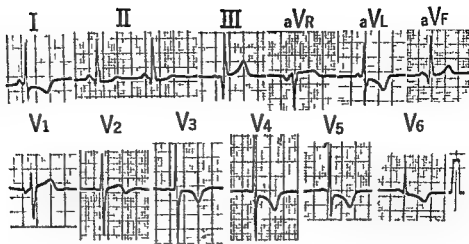


Fig 4 Transverse section of the heart A small transmural old scar is found at the posterior wall of the left ventricle and small old patches are localized along the endocardium of the lateral wall

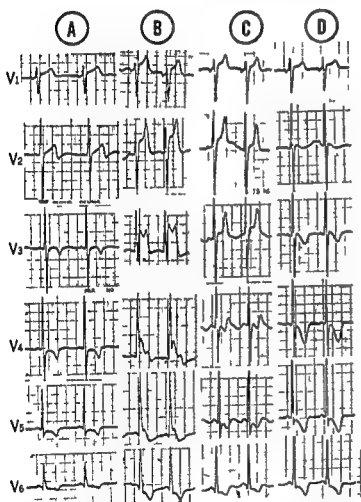
and GOT was 81 units on admission GOT was 400 units and HBD was 890 units on the following day and LDH was 2,000 units two days after admission The electrocardiogram on admission revealed QS pattern in Leads V<sub>1</sub> rS pattern in Leads V<sub>2</sub> ST segment depression in Leads II III and aV<sub>F</sub> and a slight ST segment elevation in Lead aV<sub>F</sub> (Fig 3) The electrocardiogram during attack on the following day showed Q wave and more ST segment elevation in aV<sub>F</sub> Thus this patient was diagnosed as having old anteroseptal myocardial infarction and fresh high lateral infarction

**Hospital course** Eight days after admission the patient appeared well and had no complaints Four weeks after admission, suddenly he had severe chest pain at rest and soon after he died

**Autopsy findings** A large section containing both ventricles of the heart was made (Fig 8) and the location of the infarcted area was examined An old scar was found at the anteroseptal



**Fig 1** Electrocardiogram on admission reveals abnormal Q waves in Leads II III and aV<sub>r</sub> and negative T waves in Lead I aV<sub>L</sub> and V<sub>4</sub>.



**Fig 2** A through D A Electrocardiogram on admission shows T wave inversion in Leads V<sub>1</sub> B ECG obtained during attack reveals ST segment elevation in Leads V<sub>1</sub> C ECG after administration of two doses of nitroglycerin D ECG 18 minutes after the attack reveals deep T wave inversion in Leads V<sub>1</sub>

**Laboratory findings** Blood sedimentation rate was 6 mm per hour and white blood count was 8 400/mm<sup>3</sup>. An electrocardiogram on admission revealed abnormal Q waves in Leads II III aV<sub>r</sub> and negative T waves in Leads I aV<sub>L</sub> and V<sub>4</sub> (Fig 1). This suggested old inferior myocardial infarction.

**Hospital course** After lunch on the day of admission he developed squeezing central substernal pain radiating into the left arm. This subsided only partially with two doses of nitroglycerin. The electrocardiogram obtained during the attack showed ST segment elevation in Leads V<sub>1</sub> (Fig 2B). Eighteen minutes after the attack the substernal pain subsided completely but the T waves were deeply inverted in Leads V<sub>1</sub> (Fig 2D) compared with those on admission and these findings lasted about one week. As we suspected an impending infarction we administered anticoagulant drugs and 2 tablets of isosorbide four times a day. After administration of these drugs the patient seemed to be better but the pain occasionally occurred during effort.

One month after admission at 8 07 A.M. while resting the patient suddenly developed a severe attack.

The electrocardiogram showed deeply inverted T waves in Leads V<sub>1</sub>. The pain, which was not effected by two doses of nitroglycerin, persisted for 1 hour requiring the subcutaneous administration of morphine to control it. Since we thought this state was an impending infarction he was again transferred to the CCU at 9 00 A.M. The electrocardiogram on the monitor showed ST segment depression (Fig 3A) located almost equal to Lead V<sub>1</sub> of a standard electrocardiogram. At 9 30 A.M. the patient suddenly had a severe attack. This time the electrocardiogram on the monitor revealed ST elevation (Fig 3B). Soon after ventricular fibrillation (Fig 3C) was recorded. Cardiac massage and resuscitation were applied but unfortunately were ineffective.

**Autopsy findings** No other probable cause of death than cardiac ischemia was found at complete autopsy.

After formalin fixation the heart was cut into 1 cm thick slices in order to locate and examine the location of the infarcted area. A small transmural old scar was found at the posterior wall of the left ventricle and small old patches were localized in the endocardium of the lateral wall (Fig 4).

Each main coronary artery was sectioned transversely at 3 mm throughout its entire course. The calcified segments were decalcified by immersion in 5 per cent formic acid solution for 48 hours before sectioning. Then they were inspected with a stereoscopic microscope and diagrammatically sketched. After these initial studies each segment was then dehydrated (alcohol), cleared (xylene), embedded in paraffin and transversely sectioned.

In cases where a thrombus was not detected coronary segments which showed the most severe stenosis were carefully examined by serial section. All sections were stained with hematoxylin-eosin, Masson's trichrome, Elastica van Gieson, periodic acid methenamine silver (PAM) and phosphotungstic acid hematoxylin (PTAH).

Fig 5A a section of the right coronary artery 1.2 cm from the ostium shows an almost completely occluded coronary artery except for pinhole like canalization which is thought to be an old thrombus. Figure 5B is a section from the left circumflex coronary artery at the branching site. Here severe luminal stenosis is due to layered fibrous deposition probably formed during the frequent attacks.

Fig 6A shows a section from the left anterior descending coronary artery 1 cm from the ostium. Severe luminal stenosis is mainly attributed to atheromatous deposition. Fig 6B under a higher magnification of 6A clearly shows the thinned intimal collagen fiber and infiltration of blood elements from the lumen into the atheromatous plaque through the endothelial barrier. A careful microscopic examination revealed no special changes in this arterial section which could have caused sudden death. Thus further sections around the site showing the most severe stenosis were made at intervals of 100  $\mu$ .

Fig 6C shows a section 500  $\mu$  more distal than Fig 6B. In this picture rupture of the intimal collagen fiber is found. The length of the fracture was 1800  $\mu$ , and the width was 800  $\mu$ . Discharge of the contents of the atheromatous plaque that is cholesterol clefts, foam cells and ruptured intimal collagen fiber is also observed. The ruptured ends of the intimal collagen fiber point toward the lumen at the fractured site. These findings support the belief that the fracture occurs as a result of increasing intra plaque pressure. Fibrin has already formed and surrounds the fractured intimal collagen fiber, foam cells and cholesterol clefts so the appearance of fractured intimal collagen is not due to postmortem changes.

Fig 6D shows a section 100  $\mu$  distal to that of Fig 6C. The ruptured atheromatous plaque and the formation of fibrin is more clearly seen. Fibrin and platelet aggregates adhere so strongly to the intimal collagen fiber facing the atheromatous plaque that they seem unremovable. Here the intimal collagen fiber is rough and irregular so blood cells and platelets which have entered into the atheromatous plaque from the lumen are easily broken and thus platelet aggregates and fibrin are also produced.

**Case 2** A 69 year old retired office worker entered the hospital with an 11 hour history of chest pain. Four years prior to his present illness he experienced a severe pain in the left anterior chest, admitted and diagnosed as acute antero-septal myocardial infarction. Three years after discharge he was readmitted with angina pectoris. Thereafter the pain gradually increased in severity and duration and required the administration of nitroglycerin.

Eleven hours before entry to the hospital he had a severe pain after dinner which subsided after two doses of nitroglycerin. However as chest pain reoccurred every two hours and increased in intensity he was brought to our CCU by ambulance.

**Physical examination** Blood pressure was 100/80 mm Hg heart rate was 100 beats per minute and temperature was 37°C.

**Laboratory findings** White blood count was 10500/mm<sup>3</sup>.

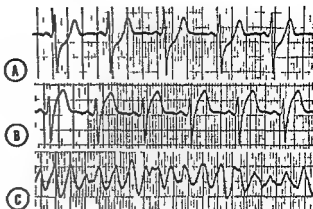


Fig 3 A through C A Electrocardiogram (made at 9 00 A.M.) on the monitor shows ST segment depression B ECG (made at 9 30 A.M.) during attack reveals ST segment elevation C Ventricular fibrillation



Fig 4 Transverse section of the heart A small transmural old scar is found at the posterior wall of the left ventricle and small old patches are localized along the endocardium of the lateral wall

and GOT was 81 units on admission. GOT was 450 units and HBD was 890 units on the following day and LDH was 2000 units two days after admission. The electrocardiogram on admission revealed QS pattern in Leads V<sub>1</sub>, rS pattern in Leads V<sub>2</sub>, ST segment depression in Leads II, III and aV, and a slight ST segment elevation in Lead aV (Fig 7). The electrocardiogram during attack on the following day showed Q wave and more ST segment elevation in aV. Thus this patient was diagnosed as having old antero-septal myocardial infarction and fresh high lateral infarction.

**Hospital course** Eight days after admission the patient appeared well and had no complaints. Four weeks after admission, suddenly he had severe chest pain at rest and soon after he died.

**Autopsy findings** A large section containing both ventricles of the heart was made (Fig 8) and the location of the infarcted area was examined. An old scar was found at the antero-septal



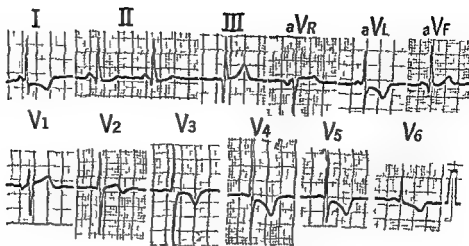


Fig 1 Electrocardiogram on admission reveals abnormal Q waves in Leads II III and aVR and negative T waves in Leads I aVL and V

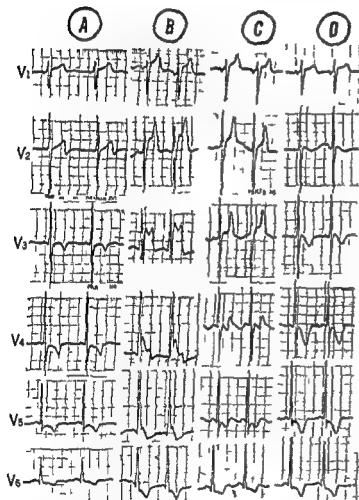


Fig 2 A through D A Electrocardiogram on admission shows T wave inversion in Leads V, B ECG obtained during attack reveals ST segment elevation in Leads V C ECG after administration of two doses of nitroglycerin D ECG 18 minutes after the attack reveals deep T wave inversion in Leads V

**Laboratory findings** Blood sedimentation rate was 6 mm per hour and white blood count was 8400/mm. An electrocardiogram on admission revealed abnormal Q waves in Leads II III aVR and negative T waves in Leads I aVL and V (Fig 1). This suggested old inferior myocardial infarction.

**Hospital course** After lunch on the day of admission he developed squeezing central substernal pain radiating into the left arm. This subsided only partially with two doses of nitroglycerin. The electrocardiogram obtained during the attack showed ST segment elevation in Leads V (Fig 2B). Eighteen minutes after the attack the substernal pain subsided completely but the T waves were deeply inverted in Leads V<sub>2</sub> (Fig 2D) compared with those on admission and these findings lasted about one week. As we suspected an impending infarction we administered anticoagulant drugs and 2 tablets of isosorbide four times a day. After administration of these drugs the patient seemed to be better but the pain occasionally occurred during effort.

One month after admission at 8:07 A.M. while resting the patient suddenly developed a severe attack.

The electrocardiogram showed deeply inverted T waves in Leads V<sub>2</sub>. The pain which was not effected by two doses of nitroglycerin persisted for 1 hour requiring the subcutaneous administration of morphine to control it. Since we thought this state was an impending infarction he was again transferred to the CCU at 9:00 A.M. The electrocardiogram on the monitor showed ST segment depression (Fig 3A) located almost equal to Lead V of a standard electrocardiogram. At 9:30 A.M. the patient suddenly had a severe attack. This time the electrocardiogram on the monitor revealed ST elevation (Fig 3B). Soon after ventricular fibrillation (Fig 3C) was recorded. Cardiac massage and resuscitation were applied but unfortunately were ineffective.

**Autopsy findings** No other probable cause of death than cardiac ischemia was found at complete autopsy.

After formalin fixation the heart was cut into 1 cm thick slices in order to locate and examine the location of the infarcted area. A small transmural old scar was found at the posterior wall of the left ventricle and small old patches were localized in the endocardium of the lateral wall (Fig 4).

Each main coronary artery was sectioned transversely at 3 mm throughout its entire course. The calcified segments were decalcified by immersion in 5 per cent formic acid solution for 48 hours before sectioning. Then they were inspected with a stereoscopic microscope and diagrammatically sketched. After these initial studies each segment was then dehydrated (alcohol) cleared (xylene) embedded in paraffin and transversely sectioned.



Fig 6 A through D Four sections of the left anterior descending coronary artery A 1.5 cm from the ostium The luminal stenosis is mainly due to atheromatous deposition (Masson's trichrome stain original magnification  $\times 25$ ) B A stronger magnification of 6A Thinned intimal collagen fiber and infiltration of blood elements into the plaque are detected (Masson's trichrome stain original magnification  $\times 50$ ) C 500  $\mu$  distal Ruptured atheromatous plaque is observed here The ruptured ends of the wall of the plaque can be seen directed toward the lumen (Masson's trichrome stain original magnification  $\times 50$ ) D 1,200  $\mu$  distal Fibrin and platelet aggregates are strongly attached to the intimal collagen fiber facing the atheromatous plaque (Masson's trichrome stain original magnification  $\times 50$ )

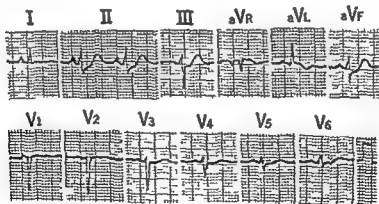


Fig 7 ECG on admission reveals QS pattern in Leads  $V_1$ ,  $V_2$ ,  $V_3$ , rS pattern in Leads  $V_4$ ,  $V_5$ ,  $V_6$ , ST segment depression in Leads II, III, and  $aVF$  and slight ST elevation in Lead  $aVL$

of yet another coagulation factor fibrin is formed and it gradually accumulates to become an occluding thrombus This idea is supported by our results which revealed that fresh occluding thrombi were formed at the site of the ruptured

atheromatous plaque in 69 of the 76 cases (90.8 per cent) Also a very small percentage of these thrombi were found to contain plaque components such as foam cells cholesterol crystals and fractured intimal collagen fiber These two find

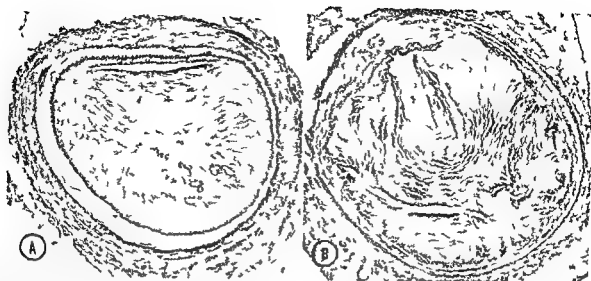


Fig 5 A and B A A section of the right coronary artery 12 cm from the ostium shows an almost completely occluded coronary artery except for pinhole like canalization (Masson's trichrome stain original magnification  $\times 20$ ) B A section from the left circumflex coronary artery at the branching site. Severe luminal stenosis is due to layered fibrous deposition (Elastic van Gieson stain original magnification  $\times 25$ )

wall of the left ventricle and relatively fresh granulation tissue was observed at the endocardium of the anterolateral wall. The former was due to the attack which occurred 4 years before admission and the latter due to that which took place 4 weeks before death. The coronary arteries were examined by the same method as in Case 1.

The left anterior descending coronary artery 2.1 cm from the ostium (Fig 9A) shows marked stenosis due to old fibrous deposition with canalization which is thought to be an old thrombus. The left circumflex coronary artery 2.4 cm from the ostium (Fig 9B) also shows marked stenosis with new canalization. The right coronary artery 3 cm from the ostium is seen in Fig 10A. The luminal stenosis is not so remarkable and atheromatous deposition is also slight. Here there seemed to be no changes in this coronary segment which could have caused sudden death. Thus further sections were made at intervals of 100  $\mu$  around the site showing the plaque hemorrhage. Fig 10B shows a section 600  $\mu$  distal to that in Fig 10A. Atheromatous deposition is larger and the infiltration of blood components is more clearly observable here. Figure 10C is of a further 600  $\mu$  distal section. The atheromatous plaque is larger than in Fig 10B. Thinned and ruptured intimal collagen fiber is found. The entry of the blood elements into the atheromatous plaque is clearly observable. Fibrin is also formed and surrounds the ruptured intimal collagen fiber foam cells and cholesterol clefts. Discharge of the atheromatous plaque into the lumen is also seen. Fig 10D shows a section 300  $\mu$  more distal. Rupture of the atheromatous plaque into the lumen is clearly demonstrable. The length of the fracture was 1200  $\mu$  and the width was 700  $\mu$ . The ruptured ends of the wall of the plaque can be seen directed toward the lumen. This suggests that the fracture occurred as a result of increasing intra plaque pressure.

## Discussion

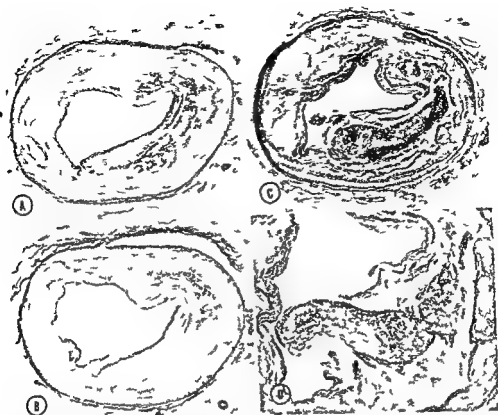
A large number of reports describing the pathological events leading to sudden or unexpected cardiac death have been published.<sup>3-11</sup> However

these results do not explain the initiating cause of acute myocardial infarction. As the clinical data are not so complete in cases of sudden death the relationship between the clinical course and the pathological findings is not fully elucidated.

Two cases where death occurred suddenly after an attack of severe chest pain were examined and the initiating cause of acute myocardial infarction compared with clinical and pathological aspects were described.

These patients had already experienced myocardial infarction before the last attack which resulted in sudden death. Thus in two of the three main coronary arteries, severe luminal stenosis with old canalization was observed. Ruptured atheromatous plaque had occurred in the third one by which the coronary flow was chiefly supplied. The ruptured ends of the abscess wall could be seen directed toward the lumen. This suggests that the increase of intra plaque pressure resulting from a honey comb like accumulation of foam cells, cholesterol clefts and blood infiltration from the lumen to the plaque through injured endothelial barrier is the cause of the rupture of the atheromatous plaque.

When this mechanical fracture has occurred platelets are exposed and become attached to the collagen. Once absorbed on the collagen, the platelets swell and release the nucleotide adenosine diphosphate,<sup>12,13</sup> which has the property of causing further adherence of the platelets. When the endothelial barrier is broken tissue thromboplastin is also released. Thus under the influence



**Fig 10** A through D Four sections of the right coronary artery A 3 cm from the ostium The luminal stenosis is not so remarkable and atheromatous deposition is also slight (Masson's trichrome stain original magnification  $\times 20$ ) B 600  $\mu$  distal Atheromatous deposition is larger and the infiltration of blood elements is more clearly observable here (Masson's trichrome stain original magnification  $\times 20$ ) C 1000  $\mu$  distal Thinned and ruptured intimal collagen fiber is found The entry of blood elements into the atheromatous plaque is clearly observable (Masson's trichrome stain original magnification  $\times 20$ ) D 1500  $\mu$  distal Rupture of the atheromatous plaque is clearly demonstrable Fibrin has already been formed The ruptured ends of the wall of the plaque can be seen directed toward the lumen (Masson's trichrome stain original magnification  $\times 40$ )

attack of preinfarction angina before that of myocardial infarction The state in which the rupture of the atheromatous plaque occurs but where the occluding thrombus has not yet been formed is the state of preinfarction angina

### Summary

Two patients who had previously experienced old myocardial infarction and who died suddenly after an attack of chest pain were examined and discussed In both cases two of the three main coronary arteries showed severe stenosis with canalization Ruptured atheromatous plaque was found in the unblocked coronary artery Fibrin was already formed and surrounded the fractured intimal collagen fiber foam cells and cholesterol clefts but a luminal thrombus had not yet been formed

Fresh occluding thrombi were formed at the site of the ruptured atheromatous plaque Coronary thrombi containing abscess components such as foam cells cholesterol clefts and the fractured intimal collagen fiber were found in our preliminary study

These views support the supposition that this fracture between the lumen and the plaque might precede and be responsible for the formation of the thrombus and the onset of acute myocardial infarction It was confirmed that the attack of preinfarction angina occurred at the time of the rupture of the atheromatous plaque

The rupture of the atheromatous plaque plays an important part as an initiating factor of preinfarction angina and myocardial infarction Thus it is necessary to examine coronary arteries by serial histopathological section method

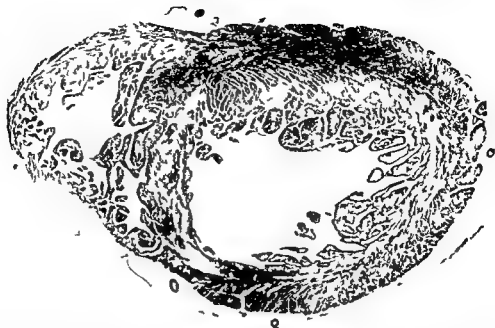


Fig 8 Large histological section containing both ventricles of the heart. An old scar is found at the antero-septal wall of the left ventricle and relatively fresh granular tissue is observed at the endocardium of the anterolateral wall (Masson's trichrome stain original magnification  $\times 3/2$ )

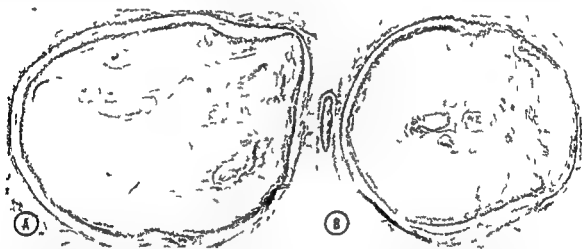


Fig 9 A and B A Left anterior descending coronary artery 2.1 cm from the ostium shows marked stenosis due to old fibrous deposition with canalization (Elastica van Gieson stain original magnification  $\times 25$ ) B Left circumflex coronary artery 2.4 cm from the ostium (Elastica van Gieson stain original magnification  $\times 20$ )

ings have been confirmed the former by many pathologists<sup>16,23</sup> and the latter by Friedman.<sup>3,4</sup>

In two cases two of the three main coronary arteries showed severe luminal stenosis. The last attack is supposed to have occurred due to the rupture of the atheromatous plaque of the third main coronary artery and this proved fatal. If these two main coronary arteries had been intact, fibrin would have been formed and gradually an occluding thrombus would have resulted after the rupture of the atheromatous plaque.

In our histopathological study,<sup>1</sup> no myocardial infarction was found in those cases where the

luminal stenosis of the coronary artery was supposed to have occurred gradually.

We have often experienced cases of myocardial infarction where the attack had occurred suddenly. Thus it requires some trigger to cause the formation of coronary thrombi and subsequent myocardial infarction.

We think this initiating factor is the rupture of the atheromatous plaque. This fracture between the lumen and the plaque might precede and be responsible for the thrombus and onset of acute myocardial infarction.

Clinically we have sometimes encountered an

# Hereditary bundle branch system defect

## Survey of a family with four affected generations

Edouard Stephan MD

Beirut Lebanon

A man presumed to have died with heart block had married three wives who in four generations engendered more than 260 members. Of the 209 family members examined 112 showed obvious abnormalities of the conducting system. Twelve showed complete right bundle branch block (RBBB), seven exhibited incomplete RBBB, six had right bundle branch block with left axis deviation, four showed RBBB with right axis deviation, one had left axis deviation alone, and two exhibited complete heart block. The pedigree pattern is compatible with the autosomal dominant mode of inheritance. The onset likely congenital and the course of the disorder are discussed.

It is now well established that in many instances disorders of the conducting system show a hereditary distribution. Since our first two reports on a Lebanese family<sup>1,2</sup> several examples have been described where various forms and degrees of block occurred in a parent and offspring or in two or more generations.<sup>3-7</sup> An autosomal dominant defect of the conducting system has been suggested.

The present family is rather unique in that it descends from a man who married three wives who engendered more than 260 members in four generations. Impairment of the intraventricular conduction predominantly the right had been documented in many individuals through three and four successive generations suggesting a hereditary defect of the bundle branch system.

From the French Faculty of Medicine, Beirut, Lebanon.

Received for publication November 18, 1976.

Accepted for publication January 5, 1977.

Reprint requests: Edouard Stephan MD, Professor of Internal Medicine, French Faculty of Medicine, Beirut, Lebanon.

## The proband

This 76-year-old man complained in March 1974 of dizziness. Examination disclosed diabetes and evidence of right bundle branch block with left axis deviation. Chest x-ray films were normal. During the following two years he was symptom free with no changes in the electrocardiograms. In February 1976 he fainted for the first time and was then found to present an intermittent complete heart block with an atrial rate of 80 to 90 a minute, a ventricular rate of 34 to 38 a minute, and QRS complexes similar to those seen when the patient was in sinus rhythm. A percutaneous pacemaker was successfully inserted.

When we realized that a half brother of the proband presented complete heart block, we decided to investigate all available members of the family.

## Family members

The proband was the eldest son of a man who married three wives with whom he had had 16 children. This man was known to suffer from heart disease with fainting attacks. He died suddenly at an advanced age, some 30 years ago. Numerous stillbirths and early deaths occurred in the second and third generations. Some members had emigrated to Africa. Therefore we could only represent in the pedigree individuals known to be alive in 1976. These numbered about 260, all progeny of the common progenitor.

Only two marriages of first cousins in the third and fourth generations were known. All others were nonconsanguineous, including the three progenitor unions.

## Method

Personal contact was established with all members living in Lebanon. The aim of the survey was explained to all responsible persons. Excellent cooperation was always obtained. Several family branches could not be entirely covered, as approach to certain remote villages in the south of the country was not always safe during the Lebanese civil war. However, a total number of 209 family members could be examined.

The survey included a clinical examination, with a 12 lead electrocardiogram and additional right precordial leads V and V<sub>1</sub> when it was necessary. Due to a shortage of x-ray films, only 18 affected persons could have a chest roentgenogram. We also had to examine 76 partners of married members of the family, including the proband's wife and partners of her

The authors wish to express their thanks to Prof Akira Kajita M D for his helpful advice in the course of this study the Pathology staff for technical assistance and the Photo section staff of the Heart Institute Japan for providing the photographs English corrections were made by Miss Barbara Levene

# REFERENCES

- 1 Hone T Sekiguchi M and Hirohara K Pathogenesis of coronary thrombosis in acute myocardial infarction A histological study of coronary arteries in 108 autopsied cases employing serial section (Abstr) Jap Circ J 40 485 1976
- 2 Yajima G New silver impregnation New method of histological study (in Japanese) Tokyo 1959 Ishiyaku Publ Co
- 3 Schwartz C J and Walsh W J Pathologic basis of sudden death Progr Cardiovasc Dis 8 465 1971
- 4 Schwartz C J and Gerry R G Anatomical pathology of sudden unexpected cardiac death Circulation 52(Suppl III) 18 1975
- 5 Perper J A Kuller L H and Cooper M Arteriosclerosis of coronary arteries in sudden unexpected death Circulation 52(Suppl III) 27 1975
- 6 Baba N Bashe W J Keller M D Geer J C and Anthony J R Pathology of atherosclerotic heart disease in sudden death I Organizing thrombosis and acute coronary vessel lesions Circulation 52(Suppl III) 53 1975
- 7 Bashe W J Baba N Keller M D Geer J C and Anthony J R Pathology of atherosclerotic heart disease in sudden death II The significance of myocardial infarction Circulation 52(Suppl III) 63 1975
- 8 Haerem J W Sudden coronary death The occurrence of platelet aggregates in the epicardial arteries of man Atherosclerosis 14 417 1971
- 9 Haerem J W Platelet aggregates in intramyocardial vessels of patients dying suddenly and unexpectedly of coronary artery disease Atherosclerosis 15 199 1972
- 10 Guthrie R B Vloder Z Nicoloff D M and Edward J E Pathology of stable and unstable angina pectoris Circulation 51 1009 1975
- 11 Spain D M and Bradess V A Sudden death from coronary heart disease Survival time frequency of thrombi and cigarette smoking Chest 58 107 1970
- 12 Hovig T Release of a platelet aggregating substance (adenosine diphosphate) from rabbit blood platelets induced by saline extract of tendon Thromb Diath Haemorrh 9 264 1963
- 13 Hovig T The effect of fibrin on platelet adherence to collagen and the subsequent aggregation reaction Fed Proc 24 155 1965
- 14 Deykin D Thrombogenesis N Engl J Med 276 699 1967
- 15 Johnson A J Recent advances in experimental thrombogenesis Fed Proc 24 827 1965
- 16 Chandler A B Chapman I Erhart L R Roberts W C Schwartz C J Sinapius D Spain D M Sherry S Ness P N and Simon J L Coronary thrombosis in myocardial infarction Report of a workshop on the role of coronary thrombosis in the pathogenesis of acute myocardial infarction Am J Cardiol 34 823 1974
- 17 Chapman I Relationship of recent coronary occlusion and acute myocardial infarction J Mt Sinai Hosp 35 149 1968
- 18 Chapman I The cause-effect relationship between recent coronary artery occlusion and acute myocardial infarction AM HEART J 87 267 1974
- 19 Sinapius D Beziehungen zwischen Koronarthrombosen und Myocardinfarcten Dtsch Med Wochr 97 443 1972
- 20 Sinapius D Zur Morphologie verschliessenden koronarthromben Dtsch Med Wochr 97 644 1972
- 21 Constantinescu P Plaque fissures in human coronary thrombosis J Atheroscler Res 1 1 1966
- 22 Friedman M and Van den Bovenkamp G J The pathogenesis of a coronary thrombosis Am J Pathol 48 19 1966
- 23 Friedman M Pathogenesis of coronary artery disease New York 1969 McGraw-Hill Book Company Inc
- 24 Friedman M The pathogenesis of coronary plaques thrombosis and hemorrhages An evaluative review Circulation 52(Suppl III) 34 1975

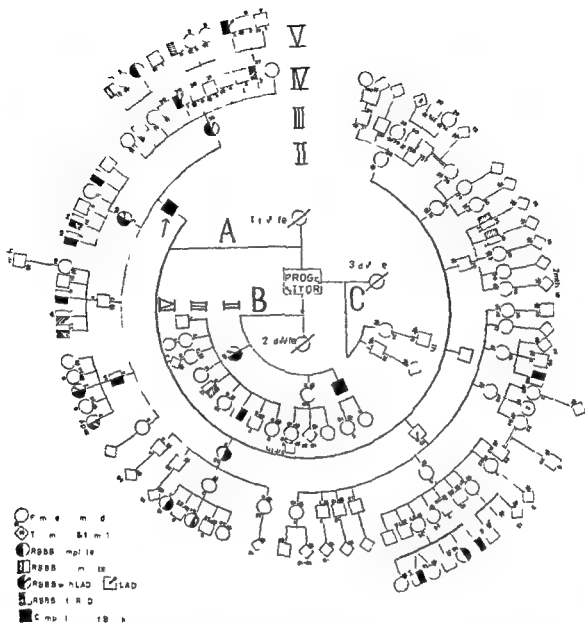


Fig 1 Pedigree of the family. The three family branches issued from the unit of the progenitor with the three wives indicated by the capital letters A, B and C; the generations denoted by Roman numerals; individual's serial number designated by Arabic numerals below circles and squares; and age by Arabic numerals above. The Proband is indicated by an arrow.

affected relatives were 98 with males 54 and females 44. Incidence is thus 33 per cent with 41 per cent males and 23 per cent females. Most cases came from the second generation and the proband progeny with a total number of 27 affected persons to 74 non affected relatives, an incidence of 48 per cent. Affected males were 15 to 11 non affected females to 13 non affected. This sex discrepancy is not significant.

Average age of all affected individuals is 33 years; it is 31 years for all offspring with first-degree affected relatives. The ratio of affected to non affected individuals in the different age groups is represented in Fig 2.

**Clinical findings.** There were many stillbirths and early deaths in the second and third generations. Two sisters A III 16 and A III 17 had ten and seven stillbirths respectively. Serology for syphilis was found negative. Later A III 17 delivered nine healthy children, one of whom A IV 88 presented RBBB. According to the family, early deaths were mainly due to common diseases of infancy and childhood and not to cardiac diseases.

No special physical finding was noted. There were three adult cases of ischemic heart disease. Fainting only occurred in the proband case. All other persons were healthy and free of



Table 1 Analysis of survey results

|  | Generation |     |     |     | Total | Sex |     | Age     |                |
|--|------------|-----|-----|-----|-------|-----|-----|---------|----------------|
|  | 2nd        | 3rd | 4th | 5th |       | M   | F   | Average | Range          |
| Number in each   | 12         | 54  | 163 | 32  | 261   | —   | —   | —       | —              |
| Number examined  | 11         | 42  | 124 | 32  | 209   | 109 | 100 | 16      | 22 days 76 yrs |
| Offspring with first degree affected relatives             | 11         | 22  | 49  | 18  | 98    | 54  | 44  | 21      | 22 days 76 yrs |
| Number   | 5          | 7   | 13  | 7   | 32    | 22  | 10  | 23      | 22 days 76 yrs |
| Per cent of offspring with first degree affected relatives | 46         | 32  | 27  | 44  | 33    | 41  | 23  |         |                |
| Sex  |            |     |     |     |       |     |     |         |                |
| Male   | 3          | 5   | 11  | 5   | 22    |     |     |         |                |
| Female   | 2          | 2   | 4   | 2   | 10    |     |     |         |                |
| Type of anomaly  |            |     |     |     |       |     |     |         |                |
| RBBB   |            |     |     |     |       |     |     |         |                |
| Complete   | 1          | 2   | 5   | 4   | 12    | 8   | 4   | 17      | 13 mos 60 yrs  |
| Incomplete   | —          | 3   | 2   | 2   | 7     | 6   | 1   | 16      | 8 mos 38 yrs   |
| With LAD   | 1          | 2   | 2   | 1   | 6     | 4   | 2   | 30      | 2 55 yrs       |
| With RAD   | —          | —   | 4   | —   | 4     | 3   | 1   | 16      | 22 days 37 yrs |
| LAD alone  | 1          | —   | —   | —   | 1     | 1   | 0   | 72      | 72 yrs         |
| Complete heart block                                       | 2          | —   | —   | —   | 2     | 2   | 0   | 58      | 41 76 yrs      |

progeny and no conduction abnormality was found in the electrocardiograms

In the present report only well defined abnormalities of the conducting system are retained. All other abnormal electrocardiographic findings were discarded.

## Results

Of the 209 family members examined 32 showed obvious electrocardiographic abnormalities related to the conducting system. They were represented by symbols in the family pedigree (Fig 1) and are listed in Table 1. They included

**Complete heart block** Two cases: the proband and his half brother B II 3.

**This case B II 3** A healthy man 41 years old experienced exertional dizziness 4 to 5 times during the last 3 years. Repeated electrocardiograms showed complete heart block with an atrial rate of 70 to 85 a minute, a ventricular rate of 35 to 38 a minute and wide QRS complexes not unlike those seen in left bundle branch block. General examination, routine laboratory analysis and chest x rays were normal. Insertion of a permanent pacemaker was not accepted.

**Right bundle branch block (RBBB)** Criteria proposed by the New York Heart Association (1966) for this diagnosis were applied. However in infants and young children a shorter QRS duration from 0.08 to 0.10 sec was accepted provided the right ventricular activation time was prolonged. Values of at least 0.06 sec were adopted by us for the diagnosis of complete RBBB and of 0.04 to 0.06 sec for incomplete RBBB.

**1st degree Complete RBBB** 12 cases. Average age 17 years (range 1 to 60 years).

A and B indicate the family branches issued from the first and second wife. Roman numerals indicate the generations. Arabic numerals the individual serial number in each generation in the pedigree.

**2nd degree Incomplete RBBB** Seven cases. Average age 16 years (range 8 months to 38 years).

**RBBB with left axis deviation (LAD)** (frontal plane axis of the initial 0.04 portion of the QRS). Six cases. Average age 30 (range 2 to 55 years). Five of these cases showed axes of  $-30^\circ$  to  $-75^\circ$ . The sixth case A II 25, a 3 year old boy showed an axis of about  $-6^\circ$ .

**RBBB with right axis deviation (RAD)** (frontal plane axis of the initial 0.04 portion of the QRS). Four cases. Average age 16 years (range 22 days to 37 years). These cases were three males A IV 2, A IV 16 and A IV 22 aged 37, 14 and 14 years respectively with axes of  $+90^\circ$  to  $+100^\circ$  and a 22 day old baby girl A IV 27 with an axis of  $+150^\circ$  (Fig 4).

**Left axis deviation (LAD)** One case: a man of 72 years with an axis of  $-75^\circ$ .

Figs 2 and 3 are examples of eight cases of RBBB of different ages and from each generation. Fig 4 shows the electrocardiogram of the 22 day old baby girl A IV 27 who to the best of our knowledge is the youngest case of RBBB ever observed in an otherwise normal subject.

There was no instance of prolongation of the PR interval. Sinus bradycardia was not encountered.

There were several borderline cases with an rS or rSr configuration in the right precordial leads without definite prolongation of the QRS (Fig 6). A few other cases showed mild degrees of left axis deviation. We also encountered several instances of the S1 S2 S3 syndrome. All these cases being ill defined or equivocal were not retained in the present series. We also discarded four young cases with deep q and tall R waves in left precordial leads because technical facilities to rule out cardiomyopathy and congenital cardiac lesion were not available.

Two first cousin marriages in the third and fourth generations resulted in 3 children with an rS pattern out of five. Incidence and distribution. The 32 affected individuals included 14 males and 10 females. Offspring with first degree

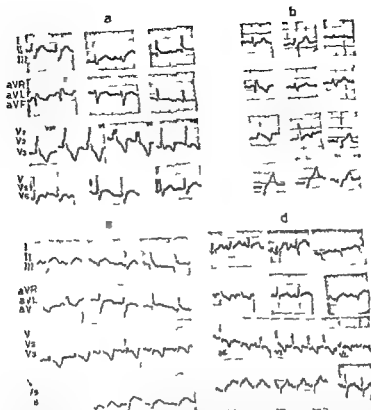


Fig 3 Four examples of RBBB in four young subjects (a) a 3-year old boy A V 8 (b) a 3-year-old girl A IV 25 (c) a 2.5-year-old girl A V 16 (d) an 8 month-old baby boy A V 10. Panels a, b and c show complete RBBB and incomplete. In d QRS duration is 0.08 sec, right ventricular activation time 0.04 sec. Axis in b is about  $\pm 30^\circ$  degrees which we consider deviated to the left for that age.

children A V 13, A V 16 and A V 17 after two skipped generations.

The 33 per cent incidence probably is below the actual one, since borderline cases have not been included. However, the expected ratio one to one in an inherited dominant trait is closely obtained in the generation of the proband and his progeny with 22 affected persons to 24 non affected individuals.

The low female incidence, though not significant, may correspond to a relatively low expressivity in females. Scrutiny of the pedigree shows indeed eight instances where affected children are born to non affected parents of whom five are females: A III 8, A III 16, A IV 9, A IV 77 and A III 14, and three males: A II 6, A III 9 and A IV 5.

Distribution according to age (Fig 5) shows a high number of affected individuals in the young age groups, with six affected to four non affected individuals between 0 and 2.5 years of age. There is no homogeneity in ages in the different genera-

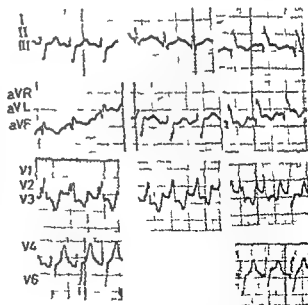


Fig 4 An instance of RBBB complete in a 22-day-old baby girl, A IV 2. QRS duration = 0.08 sec., right ventricular activation time 0.06 sec. Note the marked right axis deviation of the QRS, which could be normal for that age.

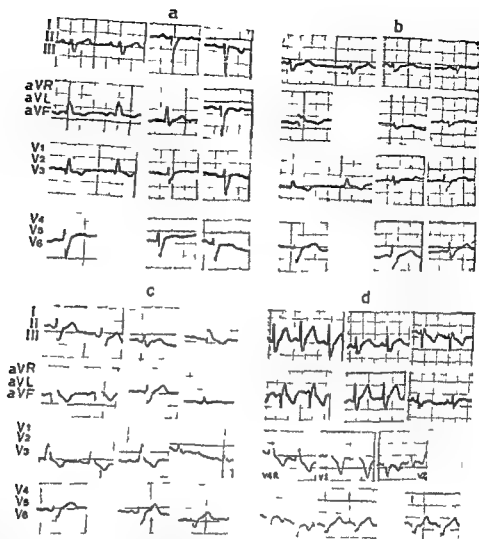


Fig 2 Four instances of RBBB from four successive generations (a) the proband in a period of sinus rhythm (b) his eldest daughter A III aged 55 (c) her eldest son A IV aged 37 (d) his third son A V aged 2 Note left axis deviation in *b* *d* and right deviation in *c*

symptoms related to the heart. With the exception of the common progenitor, no sudden death had occurred to date.

### Comment

Impairment of conduction in the right branch of His bundle is an almost constant feature of the affection in this family. The anterior division of the left branch, as indicated by left axis deviation also seems to be involved in several cases. Impairment of the posterior division is doubtful as right axis deviation in babies and young thin subjects can be normal. Development of complete heart block, as it occurred in the proband case, could represent total impairment of the two branches or the right branch and the two divisions of the left. The same development could be incriminated in subject B II 3, though heart block in this case may already have been complete from the onset of the defect.

As for borderline cases and cases with equivocal

findings not included in the series, some of them may correspond to minor forms of interventricular block, especially when encountered in offspring of affected individuals, and more particularly in parents of affected children. They will be discussed in a subsequent paper.

The pedigree pattern (Fig 1), with affected individuals, males and females through successive generations and in the absence of consanguinity, is compatible with the autosomal dominant mode of inheritance. The trait obviously had been transmitted by the common progenitor to five children from two of his three wives and down to the fourth and fifth generation in several unbroken lines. Other lineages showed skipped generations. The proband's first brother A II 3 is affected with left anterior hemiblock. None of his seven examined children were affected. Then RBBB recurred in one grandson A IV 88 after one skipped generation and in three great grand

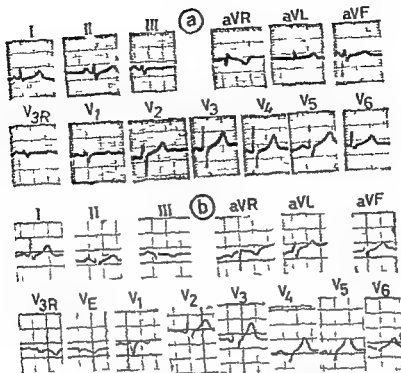


Fig 6 Minor abnormalities in two parents of affected children (a) A 26-year old woman (A IV 9) showing a double peaked r with a mild degree of left axis deviation (b) Her 31-year-old brother (A IV 5) showing an embryonic r. In both cases the time from the onset of r to the summit of r is 0.05 to 0.06 sec

proband case was that of so called chronic idio pathic heart block. A familial survey of cases of heart block would prove to be informative and of preventive value. Much also is to be known from a long follow up of this family.

We wish to thank Dr V Der Kaloustian of the Department of Pediatrics American University of Beirut for his valued advice. The author is grateful to his nephews, Robert Cook of the Department of Chemistry American University of Beirut and Ramzi Ashoush a medical student for their painstaking work in recording data and the pedigree.

#### REFERENCES

- 1 Stéphan F. Bloc auriculo-ventriculaire chez trois membres d'une même famille. *Rev Med Moyen Orient* 11: 96 1954.
- 2 Stéphan M. Bloc auriculo-ventriculaire familial. *Arch Mal Coeur* 54: 333 1961.
- 3 Conbrink J M, Davis W H and Snyman H W. Familial bundle branch block. *Am Heart J* 64: 397 1962.
- 4 Gazez P C, Culter R M, Taber E and Kelly T E. Congenital familial cardiac conduction defects. *Circulation* 32: 32 1966.
- 5 Lynch H T, Mohiuddin S, Sketch M H, Krush A J, Carter S and Hincio V. Hereditary progressive atrio-ventricular conduction defect. A new syndrome? *JAMA* 225: 1465 1973.
- 6 Morgana C M, Gray K F and Robb C H. A survey of familial heart block. *Br Heart J* 26: 683 1964.
- 7 Sarachek M S and Leonard J L. Familial heart block and sinus bradycardia. Classification and natural history. *Am J Cardiol* 29: 451 1972.
- 8 Schaal S F, Seidenstricker J, Goodman R and Wooley C F. Familial right bundle branch block, left axis deviation, complete heart block and early death. A heritable disorder of cardiac conduction. *Am Intern Med* 79: 63 1973.
- 9 Segall H N. Congenital arrhythmias and conduction abnormalities in a father and four children. *Can Med Assoc J* 85: 1283 1961.
- 10 Simonsen, M and Madsen E. G. Four cases of right sided bundle branch block and one case of atrioventricular block in three generations of a family. *Br Heart J* 32: 401 1970.
- 11 Tsagars T J, Bustamante R A and Friesendorff R A. Familial heart disease. *Dis Chest* 52: 153 1967.
- 12 Vallianos M and Siders D A. Familial conduction defects. *Cardiology* 39: 190 1974.
- 13 Waxman M W, Catching J D, Felderhof C H, Downer E, Silver M D and Abbott M. Familial atrioventricular heart block. An autosomal dominant trait. *Circulation* 51: 296 1975.
- 14 Lenégre J. Etiology and pathology of bilateral bundle branch block in relation to complete heart block. *Progr Cardiovasc Dis* 6: 409 1964.
- 15 James T N. Cardiac conduction system. *Fetal and postnatal development*. *Am J Cardiol* 25: 913 1970.
- 16 James T N, McKone H C, and Hudspeth A S. De Sanctis-Mortibus X. Familial congenital heart block. *Circulation* 51: 379 1975.
- 17 Hudson G S, Blackman M S, Rogers M C, Bharati S, and Lev M. Familial congenital bundle branch system disease. *Am J Cardiol* 32: 365 1973.

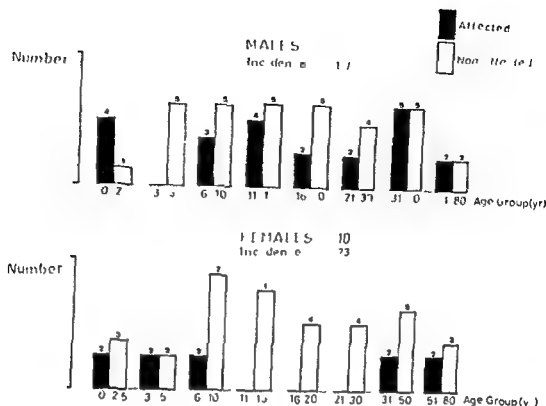


Fig 6 Age and sex distribution of affected individuals and non affected first degree relatives

tions with the exception of the fifth, where there are seven affected persons to nine non affected individuals, with an average age of two years for the affected ones. Evidently, this is an early if not congenital onset.

It has been customary to separate familial congenital block from block of late or adult onset, according to the age at which the disorder has been detected. We now recommend that no case should be considered of late or adult onset unless documented by previous normal ECGs.

Right bundle branch block associated with left anterior or posterior hemiblock is a more severe disorder than right bundle branch block alone. Both probably correspond to different degrees in the expressivity of the genetic defect, since they are encountered in the same family branches in aged as well as in young persons. One can assume that both types of block had been manifest at the same time, unless proved by serial electrocardiograms.

At the age of 76 years, the proband advanced from right bundle branch block with left anterior hemiblock to intermittent complete heart block. Progress from lesser to more advanced forms and degrees of block had been observed many times, the subject has been well reviewed.<sup>7</sup> James<sup>13</sup> looks on the region of His bundle as a locus minoris resistentiae, both electrophysiologically and in its tendency to undergo focal ischaemic degenera-

tion. In our series the bundle branch system is already affected with one or two impaired pathways. Our cases, from the beginning are in the precursor stages of heart block. Theoretically, we could presume that the conducting system, in our cases, is more vulnerable to the effect of extraneous agents such as infection, stretching and especially, deficiency in blood supply. These agents may, at any time provoke further damage and so precipitate heart block. However there are cases of heart block from birth. These cases may represent a severe degree in the expressivity of the genetic defect.

There was no clinical evidence to relate the conducting system disorder in this family to other familial or cardiovascular disease. Two recent studies<sup>14, 15</sup> demonstrated in two cases of familial heart block pathology of the distal portion of His bundle and the proximal portions of the two branches. In James case<sup>14</sup> of a 26 day old baby pathology consisted of severe caseous degeneration of these portions.

Without His bundle recordings it is not possible to indicate the site of the defect whether it is at the level of His bundle or below. Clinically we know that the defect had impaired the bundle branch system predominantly the right bundle branch.

Many individual cases presented as bilateral bundle branch disease. The evolution in the

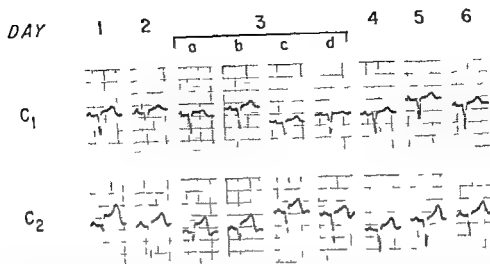


Fig 1 A 61 year old man with acute anteroseptal myocardial infarction. Note ST-segment elevation on day 1 which decreased on day 2. During an episode of chest pain on day 3 marked rise of ST segments was noted (3a). Nitroglycerin (0.4 mg) was administered for relief. Despite symptomatic response to nitrate serial maps (a to c) revealed persistent ST segment elevation which returned to the levels of day 2 one hour following the episode of chest pain. No subsequent further elevations of ST segments were observed on days 4 to 6. Enzyme values were highest on day 1 and declined thereafter. Abbreviations: C = transverse row at the fourth intercostal space and the right sternal border (equivalent of standard V lead). C = transverse row at the fourth intercostal space and the left sternal border (equivalent of standard V lead).

of ST segment elevations 15 minutes after coronary occlusion. Maroko and associates<sup>4</sup> utilizing unipolar epicardial electrograms from fixed sites of left ventricle in dogs have delineated the response of ST segment changes to various physiological and pharmacological manipulations aimed at altering the balance of local oxygen supply and demand. These experiments revealed efficacy of certain therapeutic interventions up to 6 hours following continuous coronary occlusion. Using epicardial ST segment mapping 15 minutes after coronary occlusion and estimating final extent and severity of necrosis histologically and histochemically, these workers have studied the beneficial effects on ischemic myocardial injury of propranolol, steroids, prazosin,<sup>11</sup> reperfusion of a coronary artery after 3 hours of occlusion, glucose, insulin, potassium regimen,<sup>12</sup> intra-aortic balloon counterpulsation,<sup>13</sup> hyaluronidase,<sup>14</sup> and enriched oxygen concentrations.<sup>15</sup>

Good correlation of simultaneously recorded precordial and epicardial ST segment maps in the same animals and the similarity of response of both these modalities to a variety of interventions<sup>16</sup> have encouraged clinical workers to apply precordial ST segment mapping in the study of patients with acute MI. In both epicar-

dial and precordial ST segment mapping the sums of all ST segment elevations recorded in millimeters ( $\Sigma$ ST) have been taken as an index of the magnitude of the ischemic damage and the number of areas showing ST segment elevation (NST) equal and above a certain magnitude (depending on the experimental setting and the investigator) has been taken as an index of the extent of ischemic injury.<sup>3, 17</sup> The mean ST elevation (ST) the quotient of  $\Sigma$ ST and NST has been also utilized by some workers as an index of ischemic injury of groups of animals subjected to various experimental protocols.

#### Technique of precordial ST segment mapping

Various multielectrode ECG systems comprising 35 to 72 recording sites have been employed serially in patients in the CCU.<sup>18</sup> A smaller number of electrodes have been used for the assessment of therapeutic interventions<sup>19</sup> but more data are needed to substantiate the comparability of such limited combinations of electrodes to the full multielectrode precordial map. We have been employing a 49 lead precordial mapping system (1 mV = 10 mm, paper speed 25 mm per second). A grid of seven transverse rows each consisting of seven recording sites is made on the patient's anterior thorax with a skin pencil

## Use of precordial ST-segment mapping

John E. Madias MD

Boston, Mass

With the marked reduction of morbidity and mortality rates associated with primary dysrhythmias in patients with acute myocardial infarction (MI) clinical manifestations and prognosis has been found to be closely linked to the magnitude of myocardial ischemic damage and the resultant left ventricular dysfunction.<sup>1</sup>

Early indicators of the extent of ischemic injury are therefore of paramount importance since their monitoring can be utilized for prognostication and for evaluation of techniques currently deemed effective in reducing the size of the ischemic damage.

One of such indirect early indicators of ischemic injury is the precordial ST segment mapping. Alterations of the ST segment shifts can be measured accurately and their serial recording can be utilized in the management of patients in the coronary care unit (CCU). The early appearance of changes in the electrocardiographic (ECG) ST segments in relation to the inception of coronary episode is of practical importance since interventions directed at ameliorating ischemic injury are probably more effective during the initial few hours following the onset of chest pain.

The present review is based on our experience in utilizing precordial ST segment mapping in the CCU for the follow up of patients with acute MI and the evaluation of therapeutic interventions. The usefulness and limitations of the technique and the significance of adherence to strict guidelines in using this modality is herein discussed.

From the Cardiology Division of the Department of Medicine and the Thorndike Memorial Laboratory, Boston City Hospital and Boston University School of Medicine, Boston, Mass.

Supported by United States Public Health Service Grants HL 14646, RR 533 HE 07259, Contract 71-2498 and American Heart Association Grant 74-1031.

Received for publication Jan. 7, 1976.

Reprint requests: John E. Madias MD, Cardiology Division, Boston City Hospital, Boston, Mass. 02118.

### ST segment elevation in myocardial ischemic injury

Alterations in the magnitude and distribution of ST segment shifts and changes in the direction of ST vector have been traditionally used in the clinical diagnosis of acute MI.<sup>2</sup> Although ST segment changes have been utilized only for localization of ischemic damage, an attempt for quantitation and assessment of extent of MI was made in the experiments of Prinzmetal's school, in which some correlation of the gross appearance of infarcted region and the extent of areas showing ST segment elevation at epicardial, midmural, and subendocardial levels was found.<sup>3</sup>

There is still debate as to the electrophysiologic mechanism of production of ST segment elevation, although the prevailing assumption is that both true elevation of ST segment and apparent change from downward displacement of TQ segment are responsible for the ECG curves resulting from coronary occlusion. A good correlation between the degree of epicardial ST-segment elevation and the reduction of myocardial blood flow, drop of coronary perfusion pressure,<sup>4</sup> reduction of intramyo-cardial oxygen tension, alterations in myocardial membrane action potentials,<sup>5</sup> and development of anaerobic metabolism<sup>6</sup> has been found in experiments of acute ischemic damage. Excellent correlation has also been found between ST segment elevations resulting from coronary occlusion and regional functional changes of the ischemic heart in dogs.<sup>7</sup>

More recently regional depletion of creatine phosphokinase (an excellent marker of local ischemic damage linearly correlating with segmental coronary flow) and histological and ultramicroscopic evidence of necrosis 24 hours after coronary occlusion in the dog has been found to correlate with the magnitude and extent

precordium and upper epigastrium have been utilized in the study of patients with inferior transmural MI.<sup>2</sup> We have found this application of precordial ST segment mapping to be of no practical significance. In fact often the standard 12 lead ECG showed acute current of injury in the absence of such changes in the precordial map.<sup>3</sup>

Serial precordial ST segment maps can be of help in detecting extension of MI in the absence of evidence of extension by the standard ECG. Such discrepancy between conventional ECG and precordial maps is always due to changes occurring outside the area covered by the six standard precordial leads. For the diagnosis of extension clinical and biochemical parameters of change should be used along with alterations in the ST segment maps. Map changes suggestive of extension of MI consist of further elevation in leads already manifesting ST elevation and/or new ST segment elevation of leads being previously isoelectric.<sup>3</sup> Extension of MI occurred in 57 per cent of patients with anterior MI in one study. We have also found a 48 per cent extension rate in a similar group of patients.<sup>2</sup> From the 20 patients who suffered an extension in these two studies seven patients had more than one extension.<sup>2,3</sup> This observation coupled with the timing of extension of MI (5.8 and 2.4 days after admission) suggests that interventions aimed at reducing the severity of ischemic damage in the early phase of admission should be probably followed by therapeutic manipulations directed at preventing extension of injury in the subacute phase.

The sensitivity of precordial ST segment maps in diagnosing MIs undetected by conventional ECG has not been studied heretofore. Clinical applications of the technique has been carried out in patients selected on the basis of evidence of current of injury in the standard ECG.<sup>2,3</sup> Two patients, one with lateral and one with inferior transmural MI, have been reported to have shown changes in the precordial maps in the presence of nondiagnostic 12 lead ECG. We have diagnosed the true posterior and high anterior components of a lateral MI (diagnosed by standard ECG) using maps. Leads from the posterior thorax were used to diagnose true posterior MI.

Precordial ST segment maps have been utilized in clinical studies for the evaluation of thera-

peutic interventions. Hyaluronidase,<sup>4</sup> nitroglycerin,<sup>5</sup> practolol,<sup>6</sup> propranolol,<sup>6</sup> and intra aortic balloon counterpulsation<sup>7</sup> have been found to reduce  $\Sigma$ ST and NST in patients with acute anterior MI. We have also found that oxygen administration to patients with MI resulted in reduction of  $\Sigma$ ST and NST. This change was reversed when patients returned to ambient air breathing. Combinations of interventions have also been tried.<sup>8</sup> In general such clinical applications of precordial ST segment maps consist of either serial mapping of a treated and a matched control group or serial mapping of the experimental group which is used as its own control.<sup>2,3</sup> Since alterations of  $\Sigma$ ST and NST can occur independent of application of therapeutic interventions, the importance of continually monitoring the patients' clinical status during the study period cannot be overemphasized.<sup>2,3</sup>

#### Limitations of precordial ST segment mapping

Patients with bundle branch block or implanted pacemakers cannot be studied with precordial ST segment maps since alterations of ST segments secondary to conduction abnormalities affect markedly the magnitude of ST segments.<sup>9</sup> In the presence of pericarditis also serial precordial ST segment mapping should be terminated since the technique does not yield any useful information with such complication occurring.<sup>1</sup> When a clear cut history of onset of chest pain is lacking meaningful precordial ST segment mapping cannot be carried out such absence of information hampers correlation of precordial maps with other data and results in mixing patients with infarct of different age. The technique can only be applied to patients with anterior and lateral transmural MI. Inferior transmural MI or nontransmural MI cannot be mapped.<sup>3</sup> Since the magnitude of ST segment alterations depends not only on the underlying epicardial ST segment changes but also on the electrical resistance of tissues, distance of the recording electrodes from the ischemic epicardial region, position of the heart in the chest,<sup>1</sup> projection of the infarcted area onto the anterior thoracic wall and unpredictability of boundaries of ischemic damage,<sup>2,10</sup>  $\Sigma$ ST and NST cannot be taken as quantitative measurements of underlying ischemically damaged muscle. It is probably relevant that precordial ST segment maps done in normal male volunteers produced higher  $\Sigma$ ST



and it is kept for the total hospitalization of the patients.<sup>1</sup> The first row (A) is made at the level of second intercostal space. The second row (B) is put at the third intercostal space. Rows C to G are placed at distances equal to the distance between rows A and B. Recording sites form seven vertical columns (1 to 7). Column 1 is positioned at the right sternal border and column 2 at the left sternal border. Column 5 is placed at the anterior axillary line with columns 3 and 4 spaced evenly between columns 2 and 5. Columns 6 and 7 are made at the mid and posterior axillary lines, respectively. Recordings are made via the

V lead of an ECG machine utilizing a Welsh self retaining ECG electrode (HP Part No 9301 0122) with a contact diameter of 15 mm and applying HP Redux ECG creme. Five beats or more from ECG tracings with stable baseline (no more than 1.0 mm baseline shift in five successive beats) are used in the measurement of ST deviations. ST segment deviations are measured in millimeters to the nearest 0.5 mm, 0.06 sec after the nadir of S wave using the TP segment as an isoelectric line except in cases of tachycardia when the PR segment is used instead.<sup>2</sup> This portion of ST segment has been found to be devoid of influences from atrial repolarization or QRS and T wave alterations.<sup>1</sup> Meticulous adherence to the recording techniques should be exercised. We have found that varying the location of the V' electrode by 1 cm could alter the magnitude of ST segment elevation by as much as 1.5 mm.<sup>3</sup> Except for the initial study, mapping is not carried out during chest pain episodes<sup>3, 20</sup> since recordings during post MI angina often produce marked transient ST segment alterations (Fig 1). Simultaneously with the precordial ST segment maps blood pressure, heart rate, details of patient's symptomatology, data from physical examination and information on applied therapy should be recorded and timed. Data from serial sampling of enzymes or recording of other parameters of extent of injury should be timed for proper correlation with serial ST segment maps.

#### Reproducibility and stability of the technique of ST segment mapping

Epicaudal ST segment maps done in dogs subjected to two successive 20 minute coronary occlusions 1 hour apart (for full recovery between occlusions) produced unchanged ST and NST.<sup>4</sup> Also interobserver variations in the values of ST

in precordial tracings from dogs was within 3 per cent and for NST was zero. Precordial maps done 15 minutes apart in clinically stable patients produced stable values for ST and NST.<sup>4</sup> Regarding the stability of precordial ST segment maps over time data are available. In a group of 28 consecutive patients with anterior MI studied  $0 \pm 1$  hours after onset of chest pain with two ST segment maps 1 hour apart stable ST and NST was found, except when change in the clinical status took place in the interim.<sup>2</sup> In other clinical trials in which interventions were applied the control, untreated group showed stable ST segment maps over a 2 hour period and the treated group maintained stable precordial maps in the 1 hour preceding the onset of interventions.<sup>4</sup> It cannot be overemphasized that reproducibility and stability over time of the technique is mandatory for its utilization in the assessment of currently proposed therapeutic interventions.<sup>2</sup>

#### Clinical application of precordial ST segment mapping

Precordial maps have been utilized by several workers in following patients with anterior and lateral MI.<sup>2, 10, 11</sup> A pattern of maximal ST segment elevations surrounded by smaller degrees of ST elevation has been unanimously found.<sup>2, 10, 11</sup> Variability of the gradual reduction of ST and NST has been noted with maximal change occurring in the early phase of MI.<sup>10</sup> A 29 to 31 per cent decline in the ST within the initial 24 hours has been noted.<sup>2</sup> Chest pain (Fig 1), ventricular fibrillation and reduction of arterial pressure have been found to enhance ST segment elevation.<sup>2, 11</sup> Pericarditis which produces stable high ST segment elevations has been found to invalidate the technique completely and is found quite often if sought for intensively.<sup>2</sup>

Some workers have utilized precordial ST segment depression maps in the study of anterior nontransmural MI.<sup>10</sup> Since there are no data presently available correlating ST segment depression with other markers of regional ischemic damage or necrosis further substantiation of the validity of precordial ST segment depression maps is needed.

Precordial mapping of ST segment depressions noted in the upper precordium in conjunction to ST segment elevations recorded from lower

precordium and upper epigastrium have been utilized in the study of patients with inferior transmural MI.<sup>2, 21</sup> We have found this application of precordial ST segment mapping to be of no practical significance. In fact, often the standard 12 lead ECG showed acute current of injury in the absence of such changes in the precordial map.<sup>2</sup>

Serial precordial ST segment maps can be of help in detecting extension of MI in the absence of evidence of extension by the standard ECG. Such discrepancy between conventional ECG and precordial maps is always due to changes occurring outside the area covered by the six standard precordial leads.<sup>2, 20</sup> For the diagnosis of extension clinical and biochemical parameters of change should be used along with alterations in the ST segment maps.<sup>2</sup> Map changes suggestive of extension of MI consist of further elevation in leads already manifesting ST elevation and/or new ST segment elevation of leads being previously isoelectric.<sup>2, 2</sup> Extension of MI occurred in 57 per cent of patients with anterior MI in one study. We have also found a 48 per cent extension rate in a similar group of patients. From the 20 patients who suffered an extension in these two studies, seven patients had more than one extension.<sup>2</sup> This observation coupled with the timing of extension of MI (5.8 and 2.4 days after admission) suggests that interventions aimed at reducing the severity of ischemic damage in the early phase of admission should be probably followed by therapeutic manipulations directed at preventing extension of injury in the subacute phase.

The sensitivity of precordial ST segment maps in diagnosing MIs undetected by conventional ECG has not been studied heretofore. Clinical applications of the technique has been carried out in patients selected on the basis of evidence of current of injury in the standard ECG.<sup>2, 20</sup> Two patients, one with lateral and one with inferior transmural MIs, have been reported to have shown changes in the precordial maps in the presence of nondiagnostic 12 lead ECG.<sup>2</sup> We have diagnosed the true posterior and high anterior components of a lateral MI (diagnosed by standard ECG) using maps. Leads from the posterior thorax were used to diagnose true posterior MI.<sup>2</sup>

Precordial ST segment maps have been utilized in clinical studies for the evaluation of thera-

peutic interventions. Hyaluronidase,<sup>2</sup> nitroglycerin,<sup>22</sup> practolol,<sup>23</sup> propranolol,<sup>24</sup> and intra aortic balloon counterpulsation<sup>25</sup> have been found to reduce  $\Sigma$ ST and NST in patients with acute anterior MI. We have also found that oxygen administration<sup>2</sup> to patients with MI resulted in reduction of  $\Sigma$ ST and NST. This change was reversed when patients returned to ambient air breathing. Combinations of interventions have also been tried.<sup>2</sup> In general, such clinical applications of precordial ST segment maps consist of either serial mapping of a treated and a matched control group<sup>22, 24</sup> or serial mapping of the experimental group which is used as its own control.<sup>2, 25</sup> Since alterations of  $\Sigma$ ST and NST can occur independent of application of therapeutic interventions, the importance of continually monitoring the patients' clinical status during the study period cannot be overemphasized.<sup>2</sup>

#### Limitations of precordial ST segment mapping

Patients with bundle branch block or implanted pacemakers cannot be studied with precordial ST segment maps, since alterations of ST segments secondary to conduction abnormalities affect markedly the magnitude of ST segments.<sup>2</sup> In the presence of pericarditis, also serial precordial ST segment mapping should be terminated since the technique does not yield any useful information with such complication occurring.<sup>2</sup> When a clear cut history of onset of chest pain is lacking, meaningful precordial ST segment mapping cannot be carried out, such absence of information hampers correlation of precordial maps with other data and results in mixing patients with infarct of different age. The technique can only be applied to patients with anterior and lateral transmural MI. Inferior transmural MI or nontransmural MI cannot be mapped.<sup>2</sup> Since the magnitude of ST segment alterations depends not only on the underlying epicardial ST segment changes but also on the electrical resistance of tissues, distance of the recording electrodes from the ischemic epicardial region, position of the heart in the chest,<sup>2</sup> projection of the infarcted area onto the anterior thoracic wall and unpredictability of boundaries of ischemic damage,<sup>26</sup>  $\Sigma$ ST and NST cannot be taken as quantitative measurements of underlying ischemically damaged muscle. It is probably relevant that precordial ST segment maps done in normal male volunteers produced higher  $\Sigma$ ST

than in the ones recorded from female subjects, the difference was attributed to dissimilar chest characteristics of the two groups.<sup>1</sup> It should be also emphasized that precordial ST segment maps reflect the epicardial component of MI, whereas prognosis and clinical status are influenced by the total size of the MI, which includes a substantially broader subendocardial component.<sup>2,3</sup> Despite these limitations and the lack of clinical studies correlating ST segment maps with other direct indicators of ischemic damage, this technique is useful in the monitoring of directional changes of ischemic injury as a result of natural evolution or application of therapeutic interventions. It is hoped that continuing clinical research in this exciting area will contribute to the development of a new approach in confronting the complications of power failure in the early setting of acute MI.

### Summary

Serial precordial ST segment ECG mapping with a grid consisting of 49 recording marks made on the anterior thorax of patients with acute anterior transmural myocardial infarction has been applied in the study of usefulness of this technique. It has been found that a pattern of variable devolution of the magnitude of ST segment elevations is seen in uncomplicated myocardial infarction. Extension of the infarct has been characterized by re-elevation of ST segments. Beneficial therapeutic interventions have resulted in reduction of the magnitude of ST segment elevation. However the technique cannot be applied in patients with inferior transmural myocardial infarction or in patients with functioning pacemakers, bundle branch blocks or pericarditis. The significance of adherence to strict guidelines in performing ST segment mapping and the analysis of mapping data in the light of the total clinical picture at the time of recordings is emphasized.

### REFERENCES

- Page D L, Caulfield J B, Kastor J A and DeSanctis R W. Myocardial changes associated with cardiogenic shock. *N Engl J Med* 285:133, 1971.
- Maroko P R, Libby P, Covell J W, Sobel B E, Ross J Jr and Braunwald E. Precordial ST segment elevation mapping: An atraumatic method for assessing alterations in the extent of myocardial ischemic injury. *Am J Cardiol* 29:223, 1972.
- Madias J E, Venkataraman K and Hood W E Jr. Precordial ST segment mapping. I. Clinical studies in the coronary care unit. *Circulation* 52:799, 1975.
- Massie E and Walsh T J. Clinical vectorcardiography and electrocardiography, Chicago 1969. Year Book Medical Publishers Inc.
- Rakita L, Borduas J L, Rothman S and Prinzmetal M. Studies on the mechanism of ventricular activity. XII. Early changes in the RST segment and QRS complex following acute coronary artery occlusion. Experimental study and clinical applications. *Am Heart J* 48:351, 1954.
- Samson W H and Scher A M. Mechanisms of ST segment alteration during acute myocardial injury. *Circ Res* 8:780, 1960.
- Wagner R, Segars M, Keating R P and Ward H P. Relationship between the reduction in coronary flow and the appearance of electrocardiographic changes. *Am Heart J* 38:90, 1949.
- Maroko P R, Kjekshus J K, Sobel B E, Watanabe T, Covell J W, Ross J Jr and Braunwald E. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 43:67, 1971.
- Angell C S, Lakatta E G, Weisfeldt M L and Shock N W. Relationship of intramyocardial oxygen tension and epicardial ST segment changes following acute coronary artery ligation. *Cardiovasc Res* 10:12, 1975.
- Toyoshima H, Prinzmetal M, Honba M, Kobayashi T, Mizuno Y, Nakayama R and Yamada K. The nature of normal and abnormal electrocardiograms. VIII. Relation of ST segment and T wave changes to intracellular potentials. *Arch Intern Med* 115:4, 1965.
- Scheuer J and Brachfeld N. Coronary insufficiency. Relations between hemodynamic, electrical and biochemical parameters. *Circ Res* 18:178, 1966.
- Libby P, Maroko P R, Bloor C M, Sobel B E and Braunwald E. Reduction of experimental myocardial infarct size by corticosteroid administration. *J Clin Invest* 52:599, 1973.
- Libby P, Maroko P R, Covell J W, Mallico C I, Ross J Jr and Braunwald E. The effects of pralolol on the extent of myocardial ischemic injury following experimental coronary occlusion and its effects on ventricular function in the normal and ischemic heart. *Cardiovasc Res* 7:167, 1973.
- Maroko P R, Libby P, Ginks W R, Bloor C M, Shell W E, Sobel B E and Ross J Jr. Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *J Clin Invest* 51:2710, 1972.
- Maroko P R, Libby P, Sobel B E, Bloor C M, Sybers H M, Shell W E, Covell J W and Braunwald E. The effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation* 45:1160, 1972.
- Levine I D, Maroko P R and Bernstein F F. Comparison of intra-aortic balloon pumping and left ventricular decompression on myocardial ischemic injury after experimental coronary artery occlusion. *Surg Forum* 22:149, 1971.
- Maroko P R, Libby P, Bloor C M, Sobel B E and Braunwald E. Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46:430, 1972.
- Maroko P R, Radvany P, Braunwald E and Hale S I. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation* 52:360, 1975.
- Muller J F, Maroko P R and Braunwald E. Evaluation of precordial electrocardiographic mapping as a

- means of assessing changes in myocardial ischemic injury *Circulation* 52 III 1975
- 20 Reid P R Taylor D R Kelly D T, Weisfeldt M L, Humphries J O N Ross R S and Pitt B Myocardial infarct extension detected by precordial ST segment mapping *N Engl J Med* 290 123 1974
- 21 Reid D M, Pehdes L J and Shillingford J P Surface mapping of R's T segment in acute myocardial infarction *Br Heart J* 33 30 1971
- 22 Flaherty J T Reid P R Kelly D T Taylor D R Weisfeldt M L and Pitt B Intravenous nitroglycerin in acute myocardial infarction, *Circulation* 51 137 1975
- 23 Madias J E and Hood W B Jr Precordial ST segment mapping 3 Stability of maps in the early phase of acute myocardial infarction *AM HEART J* (in press)
- 24 Maroko P R Davidson D M Libby P Hagan A O and Braunwald E Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction *Am Intern Med* 82 516 1975
- 25 Pehdes, L J Reid D S Thomas M and Shillingford J P Inhibition by  $\beta$  blockade of the ST segment elevation after acute myocardial infarction in man *Cardiovasc Res* 6 295 1972
- 26 Gold H K, Leimbach R C and Maroko P R Reduction of myocardial injury in patients with acute infarction by propranolol (abst.) *Circulation* 50(Suppl III) III 33 1974
- 27 Maroko P R Bernstein E F Libby P, DeLaria C A, Covell J W, Ross J Jr, and Braunwald E The effects of intraaortic balloon counterpulsation on the severity of myocardial ischemic injury following acute coronary occlusion Counterpulsation and myocardial injury *Circulation* 45 1150 1972
- 28 Madias J E, Madias N E and Hood W B Jr Precordial ST segment mapping 2 Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction *Circulation* 53 411 1976
- 29 Leimbach, R C Gold H K Buckley M J Austen W G., and Sanders C A Reduction of myocardial injury during acute infarction by early application of intraaortic balloon pumping and propranolol (abst.) *Circulation* 48(Suppl IV) IV 100 1973

## Concepts and applications of treadmill exercise testing and the exercise electrocardiogram

James V Faris MD  
Paul L McHenry, MD  
Stephen N Morris, MD  
*Indianapolis Ind*

Stress electrocardiography has become an integral tool in the clinical evaluation and management of patients with suspected or known cardiovascular disease. It is also commonly used as a screening procedure for normal subjects thought to be at risk of ischemic heart disease. Exercise testing with electrocardiographic monitoring was first proposed by Goldhammer and Scherf<sup>1</sup> in 1932 as an aid in the diagnosis of ischemic heart disease. Master<sup>2</sup> later developed and modified his two step test to achieve this same goal. However subsequent investigators<sup>3</sup> demonstrated that the two step test lacked sufficient sensitivity<sup>4</sup> and graded exercise testing came into common use. Other forms of stress electrocardiography have been evaluated such as induced hypoxia,<sup>5</sup> isometric exercise,<sup>6</sup> and atrial pacing.<sup>7</sup> These methods have not gained wide acceptance due to difficulties in performance and standardization as well as a lack of sensitivity and specificity.<sup>8</sup> Multistage exercise protocols have been developed for stress electrocardiography using either a motor driven treadmill or an electrically

braked bicycle ergometer. The remainder of this review will be limited to treadmill exercise testing since this is the most prevalent method of stress testing in use today.

### Pathophysiologic basis of exercise testing

Even with advanced coronary artery disease the myocardial oxygen supply may not be reduced significantly at rest to cause myocardial ischemia. The basic premise of exercise testing is to increase the myocardial oxygen requirements to unmask a reduced relatively fixed coronary blood flow. The resultant myocardial ischemia may then be detected through electrocardiographic abnormalities usually in the form of ST segment changes. Controversy still exists as to what degree of coronary arterial stenosis constitutes a significant obstructive lesion. An 85 per cent stenosis is required to decrease resting coronary blood flow in the experimental animal.<sup>9</sup> It is generally accepted that an obstruction of at least 50 per cent of the arterial lumen is necessary to cause a coronary flow restriction during exercise induced stress.<sup>10, 11</sup> Exercise leads to an increase in myocardial oxygen consumption through its augmentation of heart rate, intramyocardial tension, and the velocity of contraction of the myocardium.<sup>12, 13</sup> Increases in heart rate are associated with a fairly linear increase in myocardial oxygen consumption<sup>14, 15</sup> and the exercise heart rate provides one easily monitored parameter of myocardial oxygen requirements. By additionally monitoring the blood pressure during exercise the simple product of heart rate and systolic blood pressure can be calculated and this appears to be a practical index of myocardial oxygen requirements for the clinical laboratory.<sup>15, 16, 17</sup>

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine and the Veterans Administration Hospital, Indianapolis, Ind.

Supported in part by the Herman C. Krannert Fund and by Grants HL 06308, HL 05363 and HL 07182 from the National Heart, Lung and Blood Institute of the National Institutes of Health, United States Public Health Service, the American Heart Association, Dallas, Texas, and the American Heart Association, Indiana Affiliate.

Received for publication Jan. 11, 1977.

Reprint requests: James V. Faris, MD, Department of Medicine, Indiana University School of Medicine, Krannert Institute of Cardiology, 1100 West Michigan St., Indianapolis, Ind. 46206.

Sensitivity refers to the per cent of patients with coronary artery disease who manifest a positive stress ECG. Specificity refers to the per cent of patients who are free of coronary artery disease who have a negative stress ECG.

## Methodology

**Multistage exercise protocol** Multistage treadmill exercise protocols provide for progressive increments in work load following an initial low work load period to allow proper warm up of the patient. An example is the modified Balke protocol currently used in our laboratories (Table I). Interval increases in work load can be accompanied by changes in speed and/or grade (incline). At least three minute intervals are preferable so that steady state blood pressure and heart rate responses can be achieved. The optimal protocol should be designed to allow the patient to exercise at least three minutes without limiting symptoms to assure a functional evaluation of the patient. Protocols calling for speeds above 40 mph require patients of shorter stature to run or jog to keep pace and this often leads to an unacceptable deterioration of the ECG signal. Irrespective of which exercise protocol is routine, is utilized the treadmill speed or grade for any given stage may have to be reduced by the monitoring physician to accommodate the older patients or patients with moderately severe angina. The Bruce protocol is commonly used in part because of the availability of physiologic data which allow for an estimation of the patient's functional aerobic impairment. Using the patient's duration of exercise and a nomogram one can estimate what per cent of his predicted maximal oxygen consumption the patient was able to achieve. A failure of the patient to achieve a predicted level of exercise may be the result of cardiovascular impairment. However, a potential shortcoming of this method of assessing a patient's functional impairment is that it depends on the patient exercising to his self determined maximal capacity. Patient motivation may be an important limiting factor as can be the physician's estimation of the patient's daily activity status (sedentary, normally active, etc.).

**Electrode placement and skin preparation** The quality of the recorded ECG signal is the single most important technical aspect of exercise electrocardiography. The proper choice of electrodes and skin preparation at the site of electrode placement insure the greatest likelihood of obtaining high quality ECG records with submaximal and maximal exercise testing. In at least 10 per cent of patients with exercise induced ischemia the ST segment abnormalities will appear

**Table I** Graded multistage exercise protocol

| Exercise stage | Time (min.) | Treadmill speed (miles/hour) | Treadmill grade (%) |
|----------------|-------------|------------------------------|---------------------|
| I              | 3           | 20                           | 3                   |
| II             | 3           | 33                           | 6                   |
| III            | 3           | 33                           | 9                   |
| IV             | 3           | 33                           | 12                  |
| V              | 3           | 33                           | 15                  |
| VI             | 3           | 33                           | 18                  |
| VII            | 3           | 33                           | 21                  |

only during exercise<sup>3</sup> and excessive noise motion artifact or baseline drift may obscure the diagnostic ST segment changes. Potentially dangerous exercise induced arrhythmias may also be missed.

Adequate skin preparation consists of first cleansing the sites of electrode application with ethyl alcohol followed by removal of the superficial epidermal layer with a dental burr mounted on a high speed drill or by light abrasion with fine grain sandpaper. Too vigorous debridement should be avoided to prevent edema formation and an increase in electrical resistance at the electrode-skin interface. Once the superficial epidermal layer is loosened it should be washed away by light cleansing with acetone.

The optimal electrode is one of silver-silver chloride composition. The electrode should be one centimeter in diameter or less and encased in a lightweight plastic well which is two or three millimeters deep. This design avoids electrode contact with the skin and reduces baseline drift.

In female subjects the exercise ECG should be carried out with the patient wearing an undergarment to support the breasts. This will prevent the motion artifact caused by movement of the chest electrode by the breasts during exercise.

**Lead systems** The monitoring lead systems which will detect ischemic ST segment responses with optimal accuracy and sensitivity have not yet been clearly defined. The most commonly used lead systems are the bipolar V leads denoted CC<sub>1</sub> (right V to left V), CB (tip of right scapula to V<sub>1</sub>) or CM<sub>1</sub> (manubrium to V<sub>1</sub>). Although the CB<sub>1</sub> has the theoretical advantage of being parallel to the major ST segment vector shift during exercise, it has the practical disadvantage of excessive motion artifact and skeletal muscle noise. Blackburn reported CM<sub>1</sub> to be slightly

Table II Age predicted target heart rates\*

| Age (years) | 90% predicted maximal (beats/min) | Maximal (beats/min) |
|-------------|-----------------------------------|---------------------|
| 20          | 178                               | 200                 |
| 25          | 175                               | 196                 |
| 30          | 170                               | 191                 |
| 35          | 165                               | 187                 |
| 40          | 160                               | 180                 |
| 45          | 155                               | 176                 |
| 50          | 150                               | 170                 |
| 55          | 145                               | 167                 |
| 60          | 140                               | 160                 |
| 65          | 135                               | 156                 |

Adapted from Blackburn HW. Developments in Exercise Electrocardiography. Proceedings of the 5th Annual Meeting of the Medical Section of the American Life Convention 1969

more sensitive in detecting ST segment shifts. However the CM lead, because of its semi vertical orientation may increase the incidence of false positive tests.

In our laboratory a modified CC<sub>1</sub> lead is used for the X axis recording. The RV<sub>1</sub> position is standard while the exploring electrode (left V<sub>1</sub>) is placed somewhere between the V<sub>1</sub> and V<sub>6</sub> positions in the fifth or sixth interspaces. The placement is chosen to yield a similar large R small s (Rs) complex in all patients. This approach eliminates the problems of optimal detection of ST segment shifts caused by precordial patterns of clockwise or counterclockwise rotation. A higher interspace is selected in patients with marked left axis deviation or an electrically horizontal heart on their resting ECG. Similarly a lower interspace is selected in those patients with an electrically vertical mean QRS axis. The technician can be trained to select the optimal placement of the exploring bipolar electrode by analysis of the 12 lead ECG in the majority of patients.

The advantages of simultaneous recordings from multiple lead placements during exercise testing is still under active investigation.<sup>11</sup> To date the increase in diagnostic yield one can expect from the use of multiple leads is unclear. The authors are unaware of a completed study which has compared multiple lead placements to a single modified V<sub>1</sub> placement such as is used in our laboratories. If an increased sensitivity for detecting myocardial ischemia is demonstrated using multiple leads their widespread clinical application will be warranted, assuming specific

ity is not compromised to a degree which will nullify the value of the increase in yield. At present the technical problems inherent in orthogonal and multi lead systems make them less desirable from a practical standpoint in routine clinical treadmill testing.

**Endpoints for multistage exercise testing.** The endpoint chosen for terminating a multistage treadmill exercise test may affect the diagnostic sensitivity of the examination. In order to assure the greatest possible diagnostic yield the patient should be stressed to a near maximal level. This will also provide an adequate assessment of the patient's cardiovascular function. The exercise heart rate is an easily measured index of myocardial oxygen consumption and predicted near maximal heart rates are generally accepted as suitable endpoints.<sup>11-13</sup> Table II shows near maximal target heart rates for various age groups of normal subjects. Once the patient attains the predicted heart rate without symptoms the test can then be terminated at the discretion of the monitoring physician. When an assessment of cardiovascular function is desired some physicians favor a self determined maximal effort endpoint. When using this endpoint the monitoring physician must always assess the subjective and motivational aspects of the patient's performance to judge whether it was truly a symptom limiting maximal effort.<sup>1</sup> In the authors' opinions the physician should never insist that the patient reach a predicted heart rate or continue to a maximal effort if he is experiencing symptoms of an intensity which would prompt him to cease his daily activities. When testing patients with exertional angina to determine their exercise tolerance the onset of chest pain may be the desired endpoint. If the test is also being carried out for diagnostic purposes the time of onset of chest pain should be noted but if diagnostic ST changes are not apparent the physician should cautiously urge the patient to continue until the intensity of his angina reaches that experienced in his day to day activities. This approach may increase the yield of positive ST segment responses by as much as 15 per cent without placing the patients at added risk. The first onset of chest pain has proved to be a more practical and reproducible endpoint for serial testing in our experience. If variations in time of onset of chest pain are noted with serial testing it can usually be shown that the product of the

rate and systolic pressure has remained the same. In patients with known coronary disease who do not experience angina during treadmill testing it is generally recommended that a ceiling of 90 per cent of predicted maximal heart rate be used.

Using the above guidelines functional capacity testing of patients with coronary artery disease can be very helpful in defining their exercise tolerance levels. Exercise prescriptions and permissible work activities can then be recommended. Serial tests can also be used to assess any positive or negative effects of medical or surgical interventions.

As an epidemiological tool for screening asymptomatic subjects maximal treadmill exercise testing imposes a significantly greater cardiovascular work load than submaximal exercise and can be expected to yield a greater incidence of positive ST segment responses. In this setting the physician must be aware of the significant number of false positive responses which will occur.

**ECG and hemodynamic monitoring.** Monitoring techniques vary among different laboratories. However, there are basic requirements to insure patient safety and the capability of recording data of diagnostic value. A continuous oscilloscopic display of the exercise ECG and capability for intermittent ECG write outs are mandatory to enable proper analysis of arrhythmias and ST segment changes. The ability to monitor accurately cuff arterial pressure in the upper extremity during exercise is also necessary. In the patient with known or suspected heart disease the exercise ECG and blood pressure should be recorded at minute intervals during exercise and through at least six minutes postexercise. These parameters should always be recorded whenever symptoms, physical signs or arrhythmias develop. Emergency equipment for cardiopulmonary resuscitation, defibrillation and drug administration should be readily available. The presence of a physician knowledgeable in exercise testing is mandatory during the performance of a treadmill exercise test.

#### Safety and contraindications

Statistics reported by many exercise testing facilities document the extremely low risk of morbidity and mortality associated with multistage treadmill exercise testing. Morbidity-mor-

taity data collected by Rochmis and Blackburn<sup>3</sup> in 1971 using the multicenter questionnaire technique encompassing over 170 000 exercise electrocardiographic tests (treadmill bicycle ergometry and Masters two step) showed only 16 deaths and 40 patients requiring hospitalization for nonfatal complications. Thus the reported mortality and morbidity of exercise testing is very low. It should be noted that these risks prevail in testing facilities where exercise is carried out and supervised by experienced personnel. All patients undergoing exercise testing should have at least a basic cardiovascular history and a physical examination prior to exercise. A current 12 lead ECG is mandatory to rule out unsuspected myocardial infarction. This initial patient-physician contact serves to establish rapport and allows the physician an opportunity to explain the goals, procedures and safety of the planned exercise test to the patient. Some authorities recommend obtaining a written informed consent<sup>2</sup> while other exercise laboratories rely on verbal communication with the patient to establish implied consent. Exercise testing has enjoyed a relative freedom from associated litigation.<sup>1</sup>

The contraindications for exercise testing are listed in Table III. As noted, most of these are only relative contraindications and testing may be carried out for the elucidation of particular clinical problems using reduced work loads initially and more frequent assessments of the monitored parameters.

Indications for termination of an exercise test short of the target heart rate or limiting symptoms are listed in Table IV. Some laboratories use paired ventricular premature complexes as an indication to terminate testing. We have used the criterion of three consecutive ventricular premature complexes rather than two and have observed no complications arising from this practice. A declining heart rate or a sustained and reproducible drop in blood pressure in the face of progressive work loads suggests multivessel coronary disease with severe ischemia or cardiac failure.<sup>2</sup> A decline in these parameters is occasionally observed during the first stage of exercise in patients who are initially quite anxious and under these conditions there is no need to terminate the test. Symptoms or signs of progressive heart failure or cerebrovascular insufficiency are also indications to terminate the test. Excessive ST segment depression is a relative indication for



Table III Contraindications to exercise testing

| Absolute  | Relative   |
|---|--|
| Recent myocardial infarction or ischemic event (known or suspected) | Accelerating angina pectoris without rest pain   |
| Unstable angina pectoris with recent episodes of rest pain          | Severe valvular disease with history of syncope or failure   |
| Overt congestive heart failure                                      | Serious ventricular or supraventricular arrhythmia at rest or during previous exercise testing           |
| Serious ventricular arrhythmia at rest refractory to therapy        | Recent thrombophlebitis and/or embolism  |
|   | Active chronic (uncontrolled) systemic processes including hypertension thyroid renal or hepatic disease |
|   | Acute non cardiac illnesses  |
|   | Inordinate anxiety   |

Table IV Indications for early termination of an exercise test

## Absolute indications

- Declining blood pressure or heart rate response to progressive work loads
- Ventricular tachycardia (3 or more consecutive ventricular premature complexes)
- Ataxia or gross gait disturbances
- Vertigo or visual disturbances
- Appearance of advanced degrees of heart block
- Cyanosis or pallor

## Relative indications

- Frequent ventricular premature beats including bigeminy and multifocal ectopy
- Excessive ST segment depression
- Chest pain (see text for description)
- Inordinate anxiety
- Dizziness or unsteadiness of gait
- Supraventricular arrhythmia with rapid ventricular response
- Limiting dyspnea or fatigue

terminating exercise. Although multiple factors affect the degree of ST depression, there is a fair correlation with the severity of coronary artery disease and presumably with the extent of myocardial ischemia.<sup>1,2,3</sup> Discontinuing exercise when the ST response is definitely positive may be appropriate for diagnostic testing, although in doing so the monitoring physician may be deprived of additional information such as the

later reproduction of classical angina which would be supportive in the diagnosis of ischemic heart disease. The authors feel that irrespective of the primary purpose of the exercise test the physician should always attempt to define the patient's exercise tolerance or functional capacity, and thus the patient's limiting signs or symptoms (such as a declining blood pressure or the onset of angina) should be defined within the constraints previously outlined. If marked degrees of ST segment depression occur then the monitoring physician must make a decision concerning termination of the test based on the clinical circumstances of the individual patient.

## ECG criteria for an abnormal exercise electrocardiogram

The establishment of criteria for a positive or ischemic exercise ECG has been the subject of much investigation. However, a uniform acceptance of specific criteria still does not exist. Master's ECG criteria for a positive single stage exercise test was 0.5 mm of horizontal or down sloping ST segment depression in the postexercise recording. Later studies using coronary cineangiographic correlations established the criteria for a positive ST response as 1.0 mm or greater of horizontal ST depression which persists for at least 0.08 sec.<sup>4,5,6</sup> These criteria were found to reduce the relatively high number of false positive responses observed when only 0.5 mm of ST depression was used as a criterion. If one selects 2.0 mm of ST depression to further reduce the incidence of false positive responses, the specificity is further enhanced. However, the sensitivity of the test in patients with coronary artery disease then becomes unacceptably low.<sup>7</sup> The advent of multistage treadmill exercise testing and ECG recordings during strenuous exercise has brought about a reappraisal of the previously used postexercise ST segment criteria. It has been suggested that the analysis of the ST segment during exercise should include consideration of slowly up sloping ST depression.<sup>8,9,10,11,12</sup> Since graded exercise testing with ECG recordings during exercise results in much faster heart rates and more abbreviated ST segments, Bruce and Hornstein<sup>13</sup> have recommended that the point at which ST depression is measured be shortened from 0.08 to 0.06 sec after the J point.

The criteria currently used in our exercise

laboratories for a positive postexercise (beyond one minute recovery) ST response are 1.0 mm or greater of horizontal or downsloping ST depression. When interpreting the ST segment response during exercise or in the immediate recovery period we feel these criteria are too rigid and slow upsloping ST criteria can be utilized without compromising the specificity of the test. Computer averaging techniques are used in our laboratories to measure the ST depression and slope, but reliable measurements can be made with direct write out of the ECG at 50 mm/sec assuming high quality ECG recordings are obtained. Several investigators have reported a reduced specificity using slow upsloping ST segment criteria but these results may have been influenced by their application of the criteria to the postexercise ST segment. Preliminary evidence has been presented to suggest that the type of V monitoring lead system used may also influence the results when slow upsloping ST segment criteria are used. The findings of two recent studies evaluating the use of slow upsloping ST segment criteria during exercise (1.5 mm or > of ST depression at 80 msec beyond the J junction) seem to support the use of these criteria in the diagnostic exercise ECG.

The appearance of isolated T wave inversion during or after exercise is of no diagnostic significance as it is commonly seen in patients without disease. Robb and Marks found no increased long term mortality associated with isolated T wave negativity.

Exercise records which have normally upsloping ST segments during exercise but demonstrate horizontal or downsloping ST depression in the late recovery period merit special attention. Using computer analysis techniques for precise ST segment measurements during exercise we have found that the majority of coronary heart disease patients who demonstrate unequivocally abnormal ST depression late postexercise will have an abnormal ST Index during exercise (abnormal slow upsloping ST depression defined as 1.0 mm or greater ST depression with the ST depression in mm exceeding the ST slope in mv/sec). Patients who have a clearly normal ST Index during exercise (a normal upsloping ST segment) followed by an abnormal ST depression late postexercise are likely to have normal coronary arteriograms (Fig. 1). These patients with

false positive responses are commonly observed to have labile ST or T wave changes with hyperventilation as well. We routinely evaluate the ST segment and T wave response to voluntary hyperventilation and the standing position prior to the exercise test.

Another criterion for a positive exercise ECG is exercise induced ST segment elevation. Patients with Prinzmetal's angina demonstrate ST segment elevation during spontaneous episodes of chest pain but only a small number of these patients will manifest an abnormal exercise ST segment response. Exercise induced ST segment elevation is more commonly due to areas of abnormal myocardial wall motion as a result of previous myocardial infarction. Chahine and associates found an 86 per cent incidence of left ventricular aneurysm in patients showing exercise induced ST elevation while only 28 per cent experienced angina necessitating termination of the test.

Exercise induced U wave inversion in patients with a normal resting ECG and in the absence of left ventricular hypertrophy strongly suggests myocardial ischemia. This ECG repolarization phenomenon is more common than generally appreciated, may occur in the absence of ST segment abnormalities and in our experience is usually indicative of a significant stenosis of the left anterior descending coronary artery. The U wave inversion is difficult to detect during exercise especially at high heart rates and more often becomes apparent in the immediate recovery period when the heart rate is slowing and the baseline artifact is less. It may be a transient change and if not overlooked entirely it may be mistaken for a terminally inverted T wave. This latter differentiation can best be made by analyzing the exercise ECG before and after the appearance of the U waves to determine the true QT interval at comparable heart rates. Analysis of simultaneously recorded leads is also helpful since U wave inversion is most often isolated to horizontal or V axis leads. A right precordial lead will show reciprocal or upright U waves.

A number of medications are known to influence the ST segment response to exercise. These include digitalis, phenothiazines, quinidine and propranolol. Digitalis can cause false positive ST segment responses even in the face of a normal resting ECG. Although horizontal ST segment depression of greater than 2.0 mm has

True Positive ST  
Response Postexercise

False Positive ST  
Response Postexercise

Pt 3868

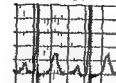
Pt 3317

Coronary Arteriograms  
LAD - 90%  
LC - 90%

Coronary Arteriograms  
Normal

Std Rest

Std Rest



Exercise (Angina)  
ST Index = -0.65

Exercise (No Angina)  
ST Index = +2.10



Three Min Rec

Three Min Rec



Six Min Rec

Six Min Rec

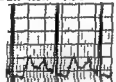
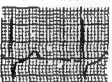


Fig 1 Examples of two patients with horizontal or down sloping ST depression in the postexercise period. The computed ST Index for the last 25 QRS complexes during exercise is shown for each patient. The ST Index is considered abnormal if the ST (J junction) depression is 1.0 mm or greater and the algebraic sum of the ST depression in millimeters and the ST slope in mv/sec is less than zero (a negative number). Patient 3868 had abnormal slow upslowing of the ST segment during exercise with an ST Index of -0.65 and coronary arteriographic studies revealed 90 per cent stenoses of the left anterior descending and left circumflex arteries. Patient 3317 presented with atypical chest pain which was not reproduced during exercise. The ST Index during exercise was +2.10 and the patient had normal coronary arteriograms.

been reported to be fairly specific for exercise-induced myocardial ischemia in patients taking digitalis," our practice has been to discontinue digitalis preparations for 10 to 14 days when possible if a diagnostic test is deemed important. Electrolyte abnormalities such as hypokalemia can also result in a false positive ST segment response during exercise. Quinidine, phenothia-

zines, and propranolol may cause a false negative ST segment response. Propranolol may cause conversion of a previously positive ST response to a negative response even when angina is still reproducible with repeat testing.<sup>28, 44</sup>

Rheumatic heart disease, left ventricular hypertrophy, Wolff Parkinson White syndrome, straight back syndrome, and mitral valve prolapse have been described as potential causes of a false positive exercise ECG.<sup>45</sup> Prolapse of the mitral valve may ultimately prove to be a common cause of otherwise unexplained false positive ST segment responses to exercise, especially in women.

When ST segment depression is present on the resting ECG, in the absence of obvious causes such as digitalis therapy, left ventricular hypertrophy, or intraventricular conduction defects, an interpretation of the ST segment response to exercise can be attempted by quantitating the magnitude of additional ST depression.<sup>28, 46</sup> In patients who present with potential cardiac symptoms, the occurrence of 1.0 mm or more of additional ST depression with exercise appears to be a fairly reliable indicator of underlying coronary artery disease.<sup>50</sup> The specificity of these criteria in asymptomatic patients who present with repolarization abnormalities at rest has not been adequately tested. In our own experience, over 50 per cent of asymptomatic subjects who demonstrate false positive ST segment responses to exercise also demonstrate labile ST or T wave changes in the postprandial state or with hyperventilation. Thus, in patients with resting ST segment abnormalities, every attempt should be made to determine if these changes are labile or fixed. Such determinations may ultimately prove to be useful aids in interpreting the clinical significance of a positive ST segment response to exercise in an asymptomatic subject.

There appears to be an increased incidence of false negative ST segment responses to exercise in patients whose resting ECG shows an old myocardial infarction pattern.<sup>47, 48</sup> However, negative conclusions concerning the usefulness of the exercise ECG as a diagnostic test based on such observations are inappropriate. In patients with unequivocal myocardial infarction patterns on their resting ECG, the diagnosis is already established and the presence or absence of ST depression with exercise will give the physician no further diagnostic information.

### Clinical value of treadmill exercise testing in the diagnosis of coronary artery disease

The multistage treadmill exercise test is clearly beneficial in the evaluation of the patient with known or suspected coronary artery disease. The reported results relative to the sensitivity and specificity of the exercise ST segment response will obviously vary according to the patient population studied. The exercise protocol used, testing endpoints, criteria for significant coronary stenosis, the monitoring lead system, and the ST segment criteria used for a positive test. The reported prevalence of abnormal ST segment responses to exercise in symptomatic patients with cineangiographically documented coronary artery disease has ranged from 54 to 85 per cent.<sup>28</sup> Virtually all of these reports dealt exclusively with horizontal or downsloping ST segment criteria and other repolarization abnormalities such as slow upsloping ST depression, ST elevation, and inverted U waves were not considered. In our own experience, one or more of these repolarization abnormalities are observed in 88 per cent of patients with exertional angina and a normal resting ECG when the patient experiences his usual chest discomfort during the exercise test. In patients presenting with a history of one or more episodes of spontaneous chest pain consistent with myocardial ischemia but not with a history of exertional angina, the likelihood of obtaining an abnormal ST response is considerably less than 88 per cent if the patient's chest pain is not reproduced during exercise. This fact is not surprising when one considers the fact that an abnormal ST segment response with exercise is a reflection of myocardial ischemia and not the coronary anatomy. The simple truth is that advanced coronary artery disease is not always associated with stress-induced myocardial ischemia.

We should emphasize at this point that the reproduction of a patient's usual chest pain during exercise is not by itself a reliable indicator of myocardial ischemia. In the absence of ST segment abnormalities, the physician should always observe for other diagnostic aids such as an abnormal blood pressure response or postexercise auscultatory changes such as a new S<sub>4</sub> gallop. Patients with coronary disease and stable exertional angina will almost always develop their chest pain at the same time of exercise or at the same heart rate  $\times$  systolic blood pressure product

with a serial testing. Patients with exercise-induced chest pain from other causes tend not to have reproducible pain patterns.

The reported incidence of false positive ST segment responses with exercise in symptomatic patients who have normal coronary cineangiographic studies has been fairly consistent at about 10 per cent.<sup>29</sup> In our laboratory, we observe false positive responses in about 7 per cent of males and 14 per cent of females with an overall incidence rate of 9 per cent. However, as stated earlier, the incidence of otherwise unexplained false positive ST responses can be reduced considerably through specific efforts to detect those patients prone to labile repolarization changes at rest. The physician may still elect to exercise these patients to evaluate their exercise tolerance or their risk for potentially significant rhythm disturbances or abnormal hemodynamic responses. However, the abnormal ST response with exercise cannot be interpreted with any degree of reliability in the presence of labile ST or T wave changes at rest. In our experience, the majority of these patients do not have significant coronary artery disease when coronary cineangiographic studies are performed.

There is a definite correlation between the number and location of arteriographically demonstrated coronary arterial lesions and the exercise ST segment response.<sup>30, 31</sup> In our series of 112 patients,<sup>1</sup> the incidence of abnormal ST segment responses on a modified V<sub>4</sub> lead system was directly proportional to the number of arteries involved ( $> 75$  per cent stenosis). All patients developed clinical angina during exercise testing and all had a normal baseline ECG. Patients with significant coronary disease confined to either the right or left circumflex coronary arteries (single vessel disease) demonstrated only a 44 per cent (8 of 18) incidence of positive ST segment responses. Those patients with isolated involvement of the left anterior descending artery showed a 77 per cent (13 of 17) incidence of positive responses. The combination of any two involved vessels increased the incidence of a positive response to 91 per cent (49 of 54). There was a 100 per cent incidence of positive responses in 23 patients with severe three vessel disease. Our incidences are slightly higher than those reported by others. The differences can probably be accounted for on the basis of our use of the computer-generated ST Index during exercise, the inclusion of only

patients with a normal resting ECG who experience angina during exercise, the use of an endpoint beyond the first appearance of chest pain and our inclusion of only patients with 75 per cent or greater coronary arterial lesions.

Thus the results of the exercise ECG must be applied to the clinical situation. A patient with a normal resting ECG no labile repolarization changes, an abnormal repolarization change with exercise and exercise induced chest pain can be expected to have significant coronary artery disease with a 95 per cent predictive accuracy. Furthermore, the majority will have multiple vessel coronary artery disease. This specificity is sufficiently high to allow further therapeutic decisions to be made on the basis of an overall assessment of the test results (exercise duration or tolerance, the exercise heart rate at onset of symptoms or ST depression, the magnitude and duration of ST depression, the blood pressure response, etc.). When the patient has an abnormal resting ECG or is on medications known to cause false positive or false negative tests, or when chest pain is not reproduced during exercise, then the reduced sensitivity and/or specificity of the ST response may limit the usefulness of the diagnostic test to varying degrees. Under these circumstances, therapeutic decisions will have to be weighted more to ward other test results or measured parameters.

In a clinically normal subject, an abnormal maximal or near maximal treadmill exercise ECG is a risk factor for the later development of overt coronary heart disease. Aronow<sup>1</sup> reported that three of 13 subjects with an abnormal ST response to exercise developed symptomatic coronary heart disease in a 30 month follow-up period. Only one of 87 subjects with a normal test developed symptomatic disease during the same follow-up period. Bruce and McDonough<sup>2</sup> and Froelicher and associates<sup>3</sup> reported a fourteen fold increase in risk for asymptomatic subjects with an abnormal ST response to strenuous exercise with five and six year follow-ups respectively. Borer and associates<sup>4</sup> and Froelicher and colleagues<sup>5</sup> reported coronary cineangiographic correlations in highly selected groups of asymptomatic subjects and found that approximately 40 per cent had significant coronary artery disease. Erickssen and co-workers<sup>6</sup> reported coronary

cineangiographic correlations on a group of clinically normal subjects more representative of the general population. They found that 64 per cent of the subjects with an abnormal ST response to exercise had significant coronary artery obstruction. The vast majority had one or more arteries involved with a 75 per cent or greater stenosis. Still, the physician must be aware that the predictive accuracy of an abnormal ST segment response to near maximal exercise in clinically normal subjects is not as great as in symptomatic patients. Furthermore, the natural history of patients with coronary artery disease manifested only by an abnormal ST response to near maximal exercise is unknown. Even if multiple vessel coronary disease is demonstrated by coronary cineangiographic studies, there is no evidence that their prognosis can be equated to the prognosis of symptomatic patients with similar pathologic anatomy. The time of onset of the ST depression along with the depth and duration of ST depression may ultimately prove to be helpful in identifying those patients at greatest near term risk. Ellestad and Wan<sup>7</sup> have shown that the duration of exercise and the exercise heart rate attainable by the patient also provide added risk factor information irrespective of the ST segment response.

Considering the currently available testing facilities, it would be virtually impossible to apply periodic treadmill exercise testing to the population in general for the purpose of detecting latent coronary artery disease. Furthermore, the cost to yield ratio would make such an undertaking impracticable even in locales where adequate facilities are available. Therefore, exercise screening of the asymptomatic population should be reserved for those subjects felt to be at greatest risk based on other clinical criteria. With rare exceptions, a positive ST segment response should be treated as another risk factor and not a definitive diagnostic finding. Intensified efforts should be undertaken to reduce other risk factors which can be altered. The subject should also be educated concerning early warning symptoms which he should promptly report to his physician. Serial exercise testing to detect new symptoms or earlier appearing and more marked ST depression may also be helpful, although the clinical value of such serial testing has not been established. The authors believe that this approach can be carried

out by the physician in keeping with the patient's best interest

### Arrhythmia detection and therapeutic evaluation

Ventricular arrhythmias at rest or during ordinary daily activities are felt to be a risk factor for future overt heart disease or sudden death.<sup>3</sup> With maximal exercise testing the prevalence of exercise induced ventricular arrhythmias in a clinically normal population is consistently between 36 and 42 per cent. In the majority of subjects the ventricular arrhythmias are in the form of rare to occasional unifocal premature ventricular complexes (PVC). The reproducibility of these arrhythmias in any given subject during serial testing is only slightly greater than by chance alone. In other words occasional PVCs may be seen in virtually any normal subject during very strenuous exercise and they are of no clinical significance. The prevalence rate of ventricular arrhythmias during maximal exercise in patients with suspected heart disease is higher, ranging from 50 to 60 per cent. These patients manifest more frequent arrhythmias at lower exercise heart rates and the arrhythmias tend to be more reproducible on serial testing. In a group of symptomatic patients with documented coronary artery disease we have shown the prevalence rate of ventricular arrhythmia to be 29 per cent during sub maximal symptom limiting exercise. When the behavior of exercise induced ventricular arrhythmias in symptomatic patients with coronary heart disease is compared with those observed in clinically normal subjects significant differences are observed. In clinically normal subjects ventricular arrhythmias are uncommon below 70 per cent of predicted maximal heart rate and frequent PVC ( $> 10/\text{min}$ ) or complex arrhythmias (multifocal or consecutive PVC) are rare at these heart rates. On the other hand frequent and complex ventricular arrhythmias at low exercise heart rates are characteristic of patients with far advanced coronary heart disease and ventricular dysfunction. Exercise induced ventricular arrhythmias alone should not be used as a criterion for the diagnosis of coronary heart disease but they may be useful diagnostic aids in the face of other abnormal parameters.

Exercise testing for ventricular arrhythmias

may ultimately prove to be most valuable in defining those patients with known coronary heart disease who are at greatest risk of future sudden death. Exercise testing and continuous ECG monitoring have both been shown to be more effective than a resting 12 lead ECG for detecting potentially lethal ventricular arrhythmias.<sup>4</sup> It is presently not clear which method is more effective especially when time and cost factors are taken into consideration. Exercise may provoke arrhythmias by producing an increased demand for myocardial oxygen consumption in patients with ischemic heart disease. This results from the exercise induced tachycardia increases in circulating catecholamines and increases in afterload. Lown and co-workers compared the effectiveness of exercise and 24 hour ambulatory monitoring for exposing patients prone to ventricular arrhythmias. They found that arrhythmias which persisted for at least two hours during continuous monitoring were also detected during exercise testing. They felt the persistent forms of ventricular arrhythmias correlated best with severe multivessel coronary artery disease. Exercise testing may therefore prove to be the more applicable method for exposing those ventricular arrhythmias which are meaningful from a prognostic standpoint.

When antiarrhythmic drugs are being used in an attempt to suppress ventricular arrhythmias serial exercise testing can be very useful in assessing adequacy of suppression. The test results are immediately available and the need for therapeutic manipulations can be determined during a single patient visit.

### Exercise testing for functional evaluation

In the clinical management of patients with known cardiac disease a quantitative measure of the patient's functional or performance capacity is most desirable. Treadmill testing is useful in this assessment. An individual's maximal exercise capacity is defined as the level of exercise required to raise his oxygen consumption ( $\dot{V}O_2$ ) to a peak value which fails to increase further with further increments in work load. The maximally attainable  $\dot{V}O_2$  ( $\dot{V}O_{2\text{max}}$ ) declines with advancing age and is reduced to varying degrees in patients with significant cardiac disease. The  $\dot{V}O_{2\text{max}}$  can be estimated by means of a nomogram which relies on data relative to the subject's age, his daily

activity status and his duration of exercise. "The subject is presumed to demonstrate a functional aerobic impairment if his duration of exercise falls short of the predicted range of normal. Unfortunately the  $\dot{V}O_{max}$  cannot be reliably predicted in individual patients with cardiac disease when symptom limiting endpoints are used." In this population the subjective discomfort which accompanies exhaustive exercise and myocardial ischemia greatly affects the patient's motivation and exercise duration.

The oxygen consumption resulting from various recreational and occupational activities has been determined. Data for oxygen consumption requirements are also available for various treadmill work loads. Using this data an individual exercise prescription can be developed for the patient with symptom limited heart disease. The prescription can be utilized to advise the patient concerning the day to day activities he should avoid as well as in outlining a therapeutic exercise training program for him.

The basal metabolic oxygen requirement for an individual has been arbitrarily designated as a unit of one MET. The increases in oxygen consumption associated with various activities are quantitated in terms of MET increases over the basal state. Patients who fall into New York Heart Association Functional Class I are able to perform oxygen consumption tasks equivalent to 6 to 10 METS without limiting symptoms. Functional Class II patients can achieve 4 to 5 METS. Class III patients 2 to 3 METS and Class IV patients 1 MET. The functional capacity of patients with organic heart disease can be estimated with a fair degree of reliability from the clinical history alone but a more reliable and quantitative estimation can often be obtained through graded exercise testing.

Multistage treadmill exercise testing is especially useful in guiding the initial therapy of a patient with ischemic heart disease and exertional angina by providing an objective measurement of his exercise tolerance time and his blood pressure and heart rate responses to exercise. A patient with only a moderate reduction in exercise time and a normal blood pressure-heart rate response can be expected to benefit from nitrate therapy alone. The patient with an exaggerated blood pressure response and/or an accelerated chronotropic response may experience a significant

improvement in symptoms with beta adrenergic blocking agents even when his initial exercise tolerance time is markedly impaired. "The appearance of an exercise induced ventricular  $S_2$  gallop or pulmonary rales after exercise usually suggests marginal ventricular compensation and may represent a contraindication to the use of beta adrenergic blocking agents. An extremely poor exercise tolerance with the onset of angina after a short duration of exercise and at a low heart rate is often associated with a poor or inadequate response to medical therapy. In general these patients should be considered as candidates for earlier coronary arteriography and possible surgical intervention. The occurrence of a sustained decline in heart rate or blood pressure during graded exercise testing is suggestive of severe multivessel coronary artery disease and acute, ischemic cardiac decompensation. Patients demonstrating these abnormalities should also be considered candidates for further diagnostic evaluation."

A comparison of the time of onset of chest pain during a baseline treadmill exercise test to that during follow up testing after a medical or surgical intervention aids in the objective evaluation of the therapeutic result. This approach has proved to be more objective and reliable than a subjective assessment of the patient's symptoms.

Stress testing is definitely contraindicated in the patient with acute myocardial infarction. However a modified exercise test using minimal work loads may be helpful in assessing residual ischemic symptoms and the capacity to perform ordinary activities in a select group of patients with myocardial infarction during their convalescent period prior to discharge. "A modified protocol should be chosen which will allow the patient to attain gradually an exercise heart rate of 60 per cent of predicted maximal not to exceed 130/minute. Prior to enrolling a recent myocardial infarction patient in a physical conditioning program a graded submaximal exercise test is advisable to document his baseline physical work capacity and to demonstrate any tendency toward exercise induced ischemia and/or arrhythmias. In the late convalescent period exercise testing can be of use to assess the patient's physical work capacity and his ability to return to employment. The demonstration of a good exer-

cise tolerance may be helpful in relieving a patient's anxieties and give him the stimulus to return to his previous level of activity

## REFERENCES

- 1 Goldhammer S and Scherf D Elektrocardiographische Untersuchungen bei kranken mit angina pectoris (Ambulatorischer Typus) Z Klin Med 122 134 1937
- 2 Master A M and Jaffe H L The electrocardiographic changes after exercise in angina pectoris Mt Sinai J Med N Y 7 679 1941
- 3 Master A M The Master two step test AM HEART J 75 609 1968
- 4 Cohen L S Elliott W C Klein M D and Gorlin H Coronary heart disease Clinical cinearteriographic and metabolic correlations Am J Cardiol 17 153 1966
- 5 Demany M A Tambe A and Zimmerman H A Correlation between coronary arteriography and the post exercise electrocardiogram Am J Cardiol 19 526 1967
- 6 McConahay D R McCallister E D and Smith R E Postexercise electrocardiography correlations with coronary arteriography and left ventricular hemodynamics Am J Cardiol 28 1 19 1
- 7 Levy R L Williams N E Bruenn H G and Carr H A The Anoxemia test in the diagnosis of coronary insufficiency AM HEART J 21 634 1941
- 8 Jackson D H Reeves T J Sheffield L T and Burdshaw J Isometric effects on treadmill exercise response in healthy young men Am J Cardiol 31 344 1973
- 9 Linhart J W Hildner F J Barold S B Lister J W and Sauer F Left heart hemodynamics during angina pectoris induced by atrial pacing Circulation 40 483 1969
- 10 Gould K L Lipscomb K and Hamilton G W Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve Am J Cardiol 33 8 1974
- 11 Rottman D Jones W B and Sheffield L T Comparison of submaximal exercise ECG test with coronary cineangiography Ann Intern Med 72 641 1970
- 12 Samoff S J Braunwald E Welch G H Jr Case R B Stauber W N and Maruz R Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension time index Am J Physiol 192 148 1958
- 13 O'Brien K P Higgs L M Glancy M I and Epstein S E Hemodynamic accompaniments of angina A comparison during angina induced by exercise and by atrial pacing Circulation 39 30 1969
- 14 Bloomquist C G Use of exercise testing for diagnostic and functional evaluation of patients with arteriosclerotic heart disease Circulation 44 1170 1971
- 15 Sheffield L T and Rottman D Systolic blood pressure heart rate and treadmill work at anginal threshold Chest 63 37 1973
- 16 Robinson B F Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris Circulation 35 1073 1965
- 17 Sheffield L T and Rottman D Stress testing methodology Progr Cardiovasc Dis 19 33 1976
- 18 Redwood D R Rowing D R Goldstein R E Besser G D and Epstein S E Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris Circulation 43 618 1971
- 19 Smokler P E, MacAlpin R N Alvaro A and Kattus A A Reproducibility of a multi stage near maximal treadmill test for exercise tolerance in angina pectoris Circulation 48 346 1973
- 20 Bruce R A Blackmon J R Jones J W and Strat C Exercise testing in adult normal subjects and cardiac patients Pediatrics 32 742, 1963
- 21 Bruce R A Kusumi F and Hosmer D Maximal oxygen intake and nonographic assessment of functional aerobic impairment in cardiovascular disease AM HEART J 85 546 1973
- 22 Bruce R A Kusumi F Niederberger M and Petersen J L Cardiovascular mechanisms of functional aerobic impairment in patients with coronary heart disease Circulation 49 676 1974
- 23 McHenry P L Philips J F and Knoebel S B Correlation of computer quantitated treadmill exercise electrocardiogram with arteriographic location of coronary artery disease Am J Cardiol 30 747 1972
- 24 Holmen M H Gillman R E Bouchard R J, Heppner R L and Warbasse J R Diagnosis of obstructive coronary disease by maximal exercise and atrial pacing Circulation 48 1227 1973
- 25 McHenry P L Fisch C Jordan J W and Corya B R Cardiac arrhythmias observed during maximal treadmill exercise testing in clinically normal men Am J Cardiol 29 331 1972
- 26 Hornsten T R and Bruce R A Computed ST forces of Frank and bipolar exercise electrocardiograms AM HEART J 78 346 1969
- 27 Blackburn H The exercise electrocardiogram Technological procedural and conceptual developments in Blackburn H ed Measurement in exercise electrocardiography Springfield Ill 1969 Charles C Thomas, Publisher pp 200-255
- 28 McHenry P L and Morris S N Exercise electrocardiography Current state of the art in Schlant R C and Hurst J W eds Advances in electrocardiography vol 2 New York 1976 Grune & Stratton Inc chap 14
- 29 Froelicher V F Thompson A J Longo M H Jr, Treibwasser J H and Lancaster M C Value of exercise testing for screening asymptomatic men for latent coronary artery disease Progr Cardiovasc Dis 18 26, 1976
- 30 Eriksson J Enge I Forfang K and Storstein O False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males Circulation 54 371 1976
- 31 Goldschlager N Selzer A and Cohn K Treadmill stress tests as indicators of presence and severity of coronary artery disease Ann Intern Med 85 777 1976
- 32 Rockman P and Blackburn H Exercise tests A survey of procedures safety and litigation experience in approximately 1 000 tests JAMA 217 1061 1971
- 33 Ladimer I Professional liability in exercise testing for cardiac performance Am J Cardiol 30 33 1972
- 34 Thompson P D and Felenkes M H Hypotension accompanying the onset of exertional angina a sign of severe compromise of left ventricular blood supply Circulation 52 23 1975
- 35 Knoebel S B Elliott W C McHenry P L and Ross E Myocardial blood flow in coronary artery disease Correlation with severity of disease and treadmill exercise response Am J Cardiol 27 51 1971
- 36 Martin C and McConahay D R Maximal treadmill



- exercise electrocardiography. Correlations with coronary arteriography and cardiac hemodynamics *Circulation* 46 956 1972
- 37 Friesinger G C and Smith R F Correlation of electrocardiographic studies and arteriographic findings with angina pectoris *Circulation* 46 1173 1972
- ✓ 38 Mason R E Likar J Biern R O and Ross R S Multiple lead exercise electrocardiography experience in 107 normal subjects and 67 patients with angina pectoris and comparison with coronary cinearteriography in 84 patients *Circulation* 36 517 1967
- 39 Sheffield L T Holt J H and Reeves T J Exercise graded by heart rate in electrocardiographic testing for angina pectoris *Circulation* 32 622 1965
- 40 McHenry P L Computer quantitation of the ST segment response to maximal treadmill exercise in Blackburn H ed *Measurement in exercise electrocardiography* Springfield Ill 1969 Charles C Thomas Publisher pp 61 71
- 41 Bruce R A and Hornsten T R Exercise stress testing in evaluation of patients with ischemic heart disease *Progr Cardiovasc Dis* 11 371 1969
- ✓ 42 McHenry P L Stowe D E and Lancaster M C Computer quantitation of the ST segment response during maximal treadmill exercise clinical correlation *Circulation* 38 691 1968
- 43 Robb G P and Marks H H Latent coronary artery disease - Determination of its presence and severity by the exercise electrocardiogram *Am J Cardiol* 13 603 1964
- 44 MacAlpin R N Kattus A A and Alvaro A B Angina pectoris at rest with preservation of exercise capacity Prinzmetals variant angina *Circulation* 47 946 1973
- 45 Chahine H A Raizner A E and Ishimori T The clinical significance of exercise induced ST segment elevation *Circulation* 54 209 1976
- 46 Lepeschkin E and Surawicz B Characteristics of true positive and false positive results of electrocardiographic Master two step exercise test *N Engl J Med* 258 511 1958
- 47 Bartel A G Behar V S Peter R H Orgain E S and Kong Y G Graded exercise stress tests in angiographically documented coronary artery disease *Circulation* 49 348 1974
- 48 Bailey I K Anderson S D Rozea P J Bernstein L Nyberg G and Korner P I Effect of beta adrenergic blockade with alprenolol on ST segment depression and circulatory dynamics during exercise in patients with effort angina *AM HEART J* 92 416 1976
- 49 Linhart J W and Turnhoff H B Maximum treadmill exercise test in patients with abnormal control electrocardiograms *Circulation* 49 667 1974
- 50 Kansal S Rotman D and Sheffield L T Stress testing with ST segment depression at rest An angiographic correlation *Circulation* 54 636 1976
- 51 Aronow W E Thirty month follow up of maximal treadmill stress test and double Master's test in normal subjects *Circulation* 47 287 1973
- 52 Bruce R A and McDonough J R Stress testing in screening for cardiovascular disease *Bull N Y Acad Med* 45 1288 1969
- 53 Borer J S Brensike J F Redwood D R Itskowitz S B Passamani E R Stone N J Richardson J M Levy R I and Epstein S E Limitations of the electrocardiographic response to exercise in predicting coronary artery disease *N Engl J Med* 293 364 1975
- 54 Ellestad M H and Wan M K C Predictive implications of stress testing Follow up of 2 700 subjects after maximum treadmill stress testing *Circulation* 51 353 1975
- 55 Hinkle L E Carver S T and Stevens M T The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle aged men *Am J Cardiol* 24 629 1969
- 56 Chang B N Perlman L V Ostrander L D and Epstein F H Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh epidemiological study *Ann Intern Med* 70 1159 1969
- 57 Fans J V McHenry P L Jordan J W and Morris S N Prevalence and reproducibility of exercise induced ventricular arrhythmias during maximal exercise testing in normal men *Am J Cardiol* 37 617 1976
- ✓ 58 McHenry P L Morris S N Kavalier M and Jordan J W Comparative study of exercise induced ventricular arrhythmias in normal subjects and patients with documented coronary artery disease *Am J Cardiol* 37 609 1976
- 59 Kosowsky B D Lown B Whiting R and Guiney T Occurrence of ventricular arrhythmias with exercise as compared to monitoring *Circulation* 44 826 1971
- 60 Crawford M O'Rourke R A Ramakrishna N Henning H and Ross J Jr Comparative effectiveness of exercise testing and continuous monitoring for detecting arrhythmias in patients with previous myocardial infarction *Circulation* 50 301 1974
- 61 Lown B Calvert A F Arrington R and Ryan M Monitoring for serious arrhythmias and high risk of sudden death *Circulation* 52(Suppl) III 189 1975
- 62 Jelinek V M Löhrbauer L A and Lown B Outpatient drug therapy for ventricular arrhythmias (Abstr) *Am J Cardiol* 31 140 1973
- 63 Bruce R A Exercise testing of patients with coronary heart disease—Principles and normal standards for evaluation *Ann Clin Res* 3 323 1971
- 64 Fox S M Naughton J P and Gorman P A Physical activity and cardiovascular health III The exercise prescription frequency and type of activity *Mod Concepts Cardiovasc Dis* 41 25 1972
- 65 Exercise testing and training of apparently healthy individuals A handbook for physicians The committee on Exercise American Heart Association New York 1972
- 66 Alderman E L Davies R O Crowley J J Lopes M G, Brooker J Z Friedman J P Graham A F Matloff H J and Harrison D C Dose response effectiveness of propranolol for the treatment of angina pectoris *Circulation* 51 964 1975
- 67 Debusk R F Houston N and Markiewicz W Prognosis of early post infarction exercise testing *Circulation* 54(Suppl II) II 9 1976
- 68 Smith J W Dennis C A Gaines J Gassmann A Marcus F I and Staman M Activity evaluation test within three weeks after myocardial infarction *Circulation* 54(Suppl II) II 10 1976

## Cardiac pacing and pacemakers IX Statistical analysis of pacemaker data

Seymour Furman MD  
Richard Whitman BEE CCE  
Bronx NY

In the recent past a variety of prosthetic medical devices such as cardiac valves and implantable cardiac pacemakers have been introduced. It has become important to analyze the duration of function of these devices as distinct from survival of the patient in whom it is implanted. The longevity of the device may be less than that of the patient or may have residual survival capacity after the patient's death. The device (especially a pacemaker) may be removed for reasons such as infection unrelated to its longevity capability.

The development of a data base of medical devices and a statistical technique for its analysis is important to ascertain longevity periods for more intense observation, prophylactic replacement and demonstrate the superiority of one model or pacing mode compared to another. Only implantable pacemakers will be the subject of this report. Because of rapid technologic development a variety of different power sources (nuclear, mercury-zinc, lithium) and different circuitry (discrete, hybrid and digital) it is important to be able to compare the performance (defined as longevity and failure pattern) of models manufactured simultaneously or successively. Further, it is important to provide the professional user with use data which is presented in an identical way and therefore allows direct comparison between different models.

Pioneering work has been done for the past ten years by a variety of workers in providing care fully recorded and analyzed data concerning pulse generator longevity. That data is even more important now because of the large number of patients and the statistical guidance required for their management. An appropriate computer data base can absorb the large amount of data, generate the analysis and provide a printout sufficiently frequently to be of real assistance in a pacemaker program.

The survival of the patient with an implanted pacemaker can be similarly defined separately from that of the pulse generator; this knowledge is invaluable to ascertain the longevity requirement of pacemakers to be manufactured.

Each pulse generator implanted at Montefiore Hospital and Medical Center is recorded by model and serial number, its date of implant and explant and the patient in whom implanted. The generator is followed throughout its duration in the patient and upon removal is analyzed. The cause for removal is then coded; four possibilities of explant exist:

1 The patient may have died and the pacer is known to be functioning normally or at least is not believed to have caused the patient's death. A major effort is made in all deaths to ascertain cause and the involvement if any of the pacemaker. The pacer is credited with normal function for its period of use and is then removed from the series.

2 The patient lost to follow up is a circumstance treated as No. 1 above with the date of loss assigned to determine a period of known normal function.

3 The pacer has been replaced but not because

From the Department of Surgery, Cardiothoracic Division, Montefiore Hospital and Medical Center, Bronx, NY.  
Supported in part by United States Public Health Service Grant 5 R01 HL-04457-16.

Received for publication Oct 1977

Reprint request: Seymour Furman, MD, Montefiore Hospital and Medical Center, 555 East 105th Street, Box 12, 10477.

DR SEYMOUR FURMAN S FACEMAKER FILE MODEL 143A LISTED ON 11/75/75

| UNIT # | PATIENT         | IMPLANTED | EX-PLANTED | CODE      |
|--------|-----------------|-----------|------------|-----------|
| 101    | H [REDACTED] II | 6/23/69   | 11/2/71    | I-IIAT    |
| 107    | K [REDACTED] A  | 7/15/69   | 8/19/71    | D-IIAT    |
| 108    | A [REDACTED] I  | 7/17/69   | 9/27/71    | D-IIAT    |
| 102    | W [REDACTED] R  | 7/24/69   | 3/23/71    | D-IIA     |
| 118    | N [REDACTED] M  | 7/29/69   | 9/22/71    | D-IIA     |
| 112    | A [REDACTED] II | 7/29/69   | 7/1/71     | D-IIA     |
| 137    | B [REDACTED] A  | 8/14/69   | 1/1/71     | L-?       |
| 116    | H [REDACTED] F  | 8/22/69   | 1/7/71     | D-IIAT    |
| 104    | R [REDACTED] J  | 9/4/69    | 8/17/71    | D-IIAT    |
| 150    | K [REDACTED] C  | 9/18/69   | 12/8/71    | E-IIC     |
| 144    | H [REDACTED] R  | 9/25/69   | 7/15/71    | I-IIAT    |
| 170    | H [REDACTED] A  | 9/26/69   | 5/26/77    | D IIAT    |
| 146    | S [REDACTED] F  | 10/3/69   | 8/1/70     | R-CEASED  |
| 39     | Z [REDACTED] K  | 11/10/69  | 4/4/72     | D IIAT    |
| 170    | B [REDACTED] C  | 11/11/69  | 8/18/72    | D-IIAT    |
| 223    | G [REDACTED] K  | 11/13/69  | 6/5/74     | D-IIAT    |
| 177    | L [REDACTED] H  | 1/6/70    | 4/12/73    | D-IIAT    |
| 194    | F [REDACTED] I  | 1/9/70    | 1/1/71     | L ?       |
| 184    | L [REDACTED] A  | 1/9/70    | 8/1/73     | D-IIAT    |
| 33     | T [REDACTED] I  | 2/17/70   | 1/7/72     | R-IID     |
| 183    | M [REDACTED] G  | 1/26/70   | 8/25/72    | D-IIAT    |
| 198    | S [REDACTED] S  | 1/13/70   | 1/7/72     | D-IIAT    |
| 321    | N [REDACTED] M  | 2/5/70    | 4/6/70     | II CEASED |
| 330    | R [REDACTED] II | 2/6/70    | 12/5/71    | D-IIAT    |
| 144    | H [REDACTED] B  | 2/12/70   | 3/30/73    | D-IIAT    |
| 438    | K [REDACTED] P  | 3/2/70    | 7/5/72     | D IIA     |
| 393    | D [REDACTED] J  | 3/4/70    | 3/19/71    | D-IIA     |
| 142    | C [REDACTED] E  | 3/5/70    | 7/16/71    | R-IIA2    |
| 248    | B [REDACTED] E  | 3/10/70   | 10/23/70   | R-CEASED  |
| 349    | M [REDACTED] J  | 3/12/70   | 1/4/73     | D IIAT    |

Fig 1 Computer generated pacemaker file for Cordis ventricular inhibited model 143A now obsolete. Each unit is listed by serial number, name of patient in whom implanted, dates of implant and explant, and explant code. D is removal for generator failure. IAT = cessation of pacing detected by telephone. IAS = major pacing change (i.e. rate change by more than 10 BPM) but with consistent capture detected in pacer clinic. IIA = impending failure detected in pacer clinic. IIAT = impending failure detected via telephone monitoring. L = lost to follow up at the date indicated. R = removed for reasons other than pacer failure. R ceased = patient died, pacer functioning. E = electively removed—no pacer failure.

DR SEYMOUR FURMAN S LIFE TABLE FOR PACER MODEL 143A CALCULATED 11/22/75

| AGE MONTHS | NUMBER ENTER | ---REMOVALS---<br>FAIL ELCTV UNFL | LOST TO<br>FOLLOW UP | TO PART<br>EXPLD | % SURVIVAL RATE<br>INTERVAL | % SURVIVAL RATE<br>CUMULATIVE | STANDARD<br>ERROR |
|------------|--------------|-----------------------------------|----------------------|------------------|-----------------------------|-------------------------------|-------------------|
| 0 - 3      | 100          | 0                                 | 0                    | 0                | 100                         | 100                           | 0                 |
| 3 - 6      | 97           | 0                                 | 0                    | 4                | 100                         | 100                           | 0                 |
| 6 - 9      | 92           | 1                                 | 0                    | 3                | 98.895                      | 98.895                        | 1.09885           |
| 9 - 12     | 88           | 0                                 | 0                    | 1                | 100                         | 98.895                        | 1.09885           |
| 12 - 15    | 87           | 2                                 | 0                    | 1                | 97.6878                     | 96.6084                       | 1.92511           |
| 15 - 18    | 84           | 2                                 | 1                    | 4                | 97.5308                     | 94.2229                       | 2.51001           |
| 18 - 21    | 76           | 3                                 | 0                    | 1                | 96.0265                     | 90.4789                       | 3.0877            |
| 21 - 24    | 72           | 4                                 | 1                    | 2                | 94.3262                     | 83.1454                       | 3.9116            |
| 24 - 27    | 65           | 5                                 | 2                    | 3                | 90.4                        | 71.1222                       | 4.76232           |
| 27 - 30    | 54           | 7                                 | 0                    | 3                | 87.6666                     | 66.0651                       | 5.48934           |
| 30 - 33    | 44           | 6                                 | 0                    | 0                | 86.3636                     | 57.7472                       | 6.86893           |
| 33 - 36    | 38           | 5                                 | 0                    | 1                | 86.6666                     | 50.0475                       | 6.01227           |
| 36 - 39    | 32           | 7                                 | 0                    | 1                | 77.7777                     | 38.9708                       | 5.96740           |
| 39 - 42    | 21           | 3                                 | 0                    | 1                | 86.1905                     | 33.8485                       | 5.86504           |
| 42 - 45    | 17           | 4                                 | 0                    | 0                | 77.7777                     | 26.3665                       | 5.64008           |
| 45 - 48    | 13           | 3                                 | 0                    | 0                | 77                          | 17.744                        | 5.35935           |
| 48 - 51    | 8            | 4                                 | 0                    | 0                | 50                          | 7.87248                       | 4.40045           |
| 51 - 54    | 4            | 1                                 | 1                    | 1                | 66.6666                     | 6.58165                       | 3.97818           |
| 54 - 57    | 1            | 1                                 | 0                    | 0                | 0                           | 0                             | 0                 |

39 30 6 100

Fig 2 Life table tabulation by 3 month intervals for Cordis 143A. All implanted are entered at time zero. Each unit removed is listed as failed, elective or unrelated. The per cent survival rate is listed for the interval, i.e. the per cent of those units entering an interval which leave it intact. The cumulative survival rate is that for the entire series. The duration in months of one standard error is listed.

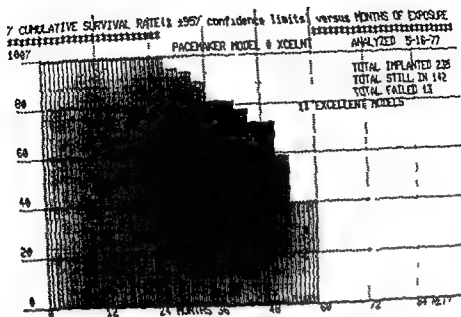


Fig 3 Excellent — One hundred per cent survival for 24 months. With onset of failures the  $\pm$  standard error limits are indicated. There is 40 per cent cumulative survival rate at 54 months after implant and a 40 per cent rate at the end of 84 months (Unretouched photograph from cathode ray tube screen)

of failure perhaps for infection or change in pacing, mode this possibility too is treated as No 1 above

4 The pacer has failed and has been removed or (rarely) has caused the patient's death (The pacer is credited with normal function and then failure)

Another code (S) is that for *continued function* in a living patient. When all generators have been removed this coding no longer exists for a series.

It is important that the derivation of this data be based on and be supported by an extensive and careful follow up technique (see Cardiac Pacing Pacemakers VIII) in which patients are monitored as carefully as possible, each event is evaluated and each removed unit is analyzed in an electronics laboratory to ascertain function and assess the accuracy of clinical judgement.

A short printout is provided to the pacemaker staff monthly. Additional data are available at all times (though the computer is not on line it is controlled by the pacemaker staff) and specific comparisons not routinely provided are made available as necessary. All pulse generators used at Montefiore Hospital and Medical Center since mid 1969 are included in the data base. The

monthly printout is only of those models with units still implanted and functioning though older inactive models are retained in the data base and the data are retrieved as necessary.

More than 80 different models from 13 different manufacturers encompassing over 2300 pulse generators have been recorded. Data is updated weekly and calculated on a monthly basis. In addition to the abbreviated monthly printout a more complete printout is provided quarterly which includes the full data base and analysis and is provided to all pacemaker surgeons, cardiologists, nurses and engineers. Each manufacturer is provided with his own data (and his own data only) quarterly.

The monthly and quarterly analyses include

1 A printout of all pulse generators listed by model and serial number, date of implant and explant and reason. Each pulse generator is listed individually (Fig 1)

2 A verification list of all pulse generators by ascending duration of implantation

3 A life table with the cumulative survival rates, the interval survival rates and standard errors (Fig 2)

4 A graphic display of the life table with 95 per cent confidence limits

# Mathematical and computation technique

Various statistical analyses have been used to record analyze and estimate pulse generator longevity. We have used the actuarial method which has earlier been used to evaluate the longevity of prosthetic cardiac valves and cardiac pacemakers.<sup>8,10</sup> Since the beginning of the computerization program during September, 1974, a similar statistical method has been adopted by the Association for the Advancement of Medical Instrumentation as a suggested standard.<sup>11</sup> The calculations are similar except for that of the lower confidence limit.

The actuarial method accurately estimated the depletion of a population in time. The estimator of survival is the *CUMULATIVE SURVIVAL RATE* at any desired time and that in turn is based upon *INTERVAL SURVIVAL PROPORTIONS*,  $P(k)$  as defined

$$P(k) = 1 - \frac{D(k)}{N(k) - \frac{S(k) + L(k) + R(k) + E(k)}{2}}$$

where  $D$  = number failures (either battery exhaustion or electronic failure) in  $K$ th interval

$N$  = number entering the  $K$ th interval,

$L$  = number lost to follow up in  $k$ th interval

$E$  = number electively removed in  $K$ th interval

$R$  = number non pacemaker related failures in  $K$ th interval

$S$  = number surviving an incomplete interval

and  $h$  = quarterly interval since implantation

The *CUMULATIVE SURVIVAL RATE*  $Q(k)$  is equal to the product of all previous Interval Survival Proportions or mathematically

$$Q(k) = P(1) \times P(2) \times P(3) \times \dots \times P(k) \times 100$$

Therefore the *CUMULATIVE SURVIVAL RATE* is the probability of a pacemaker surviving to a particular time based on the previously observed survival experience. This method offers a precise means of estimating the  $K$ th quarterly *SURVIVAL PROPORTION* by utilizing information from patients with less than  $K$  quarterly intervals of experience. Two assumptions have been adopted. One is that pacemakers *LOST TO FOLLOW UP* are presumed to have the same natural history as those still followed. With this

assumption the maximum information is extracted from the raw data without biasing the results toward or against the actual longevity. Another assumption is that pacemakers surviving an incomplete interval contribute on the average one half an interval of experience. This assumption is justified by the equal distribution of implantation and removal of pacemakers over each three month interval. The primary result of these statistics is the *LIFE TABLE* (Fig. 2). It consists of a compilation of all data necessary to compute the *CUMULATIVE SURVIVAL RATES* and is tabulated in quarterly intervals. The Standard Error of the Cumulative Survival Rate is an estimate of precision for the corresponding quarterly Cumulative Survival Rate. The Standard Error  $SE(Q(k))$  is defined

$$SE(Q(k)) = Q(k) \times \sqrt{\frac{1-P(1)}{N(1)} - \frac{S(1)+L(1)+E(1)+R(1)-D(1)}{2N(1)} + \frac{1-P(k)}{N(k)} - \frac{S(k)+L(k)+E(k)+R(k)-D(k)}{2N(k)}}$$

Another result, the *SURVIVAL CURVE* is a plot of the *CUMULATIVE SURVIVAL RATE* against exposure time. The *SURVIVAL CURVE* is valuable because of its visual impact, especially when two curves are compared and the 95 per cent confidence limits are indicated.

We use the Normal Theory to define the 95 per cent *CONFIDENT LIMITS* as

$\pm 95\% C.L. = \pm 2 \times \text{STANDARD ERROR}(K)$   
The results are comparable to the AAMI Technique when the data base is over 20 units.

All data and calculations are on a PDP 8 E minicomputer\* equipped with 32K of core memory, an RK8E Disk, a TD8E Dectape and LA 36 printer and a VT 55 graphics terminal. The programs are written in the Basic language under the OS 8 operating system.

## Comparison of pulse generator quality

Analysis of the longevity of implanted cardiac pacemakers is required to evaluate the operational characteristics of competing power sources and to establish a criterion of manufacturing quality independent of features and based on specific longevity and failure characteristics.

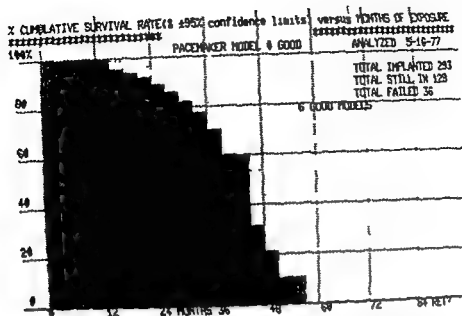


Fig 4 Good = Failure begins earlier than in the excellent series and continues more rapidly. There is 50 per cent survival 48 to 51 months after implant. No units have reached the sixtieth month. (Unretouched photograph from cathode ray tube screen.)

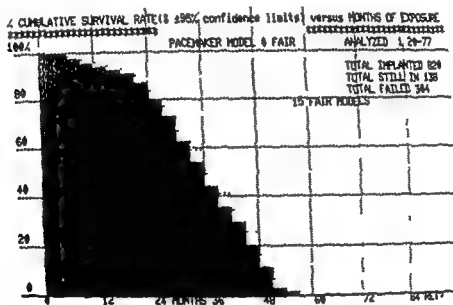


Fig 5 Fair = Failures appear after the first six months of implant and the cumulative survival falls rapidly. There is 50 per cent survival 36 to 39 months after implant. All units have failed by the 57 to 60 month. (Unretouched photograph from cathode ray tube screen.)

These characteristics include the absence of early failures when power capacity should not be a factor, the appearance of the first wear out failures and the magnitude of the ongoing or "random" failure rate.

To ascertain the level of quality of pacemakers implanted since 1969, four levels of quality were

established arbitrarily. The data are relevant as of May 1977.

These are

**Excellent** The pulse generator model should demonstrate 100 per cent function for at least 24 months (Fig 3).

**Good** Ninety eight per cent cumulative survival

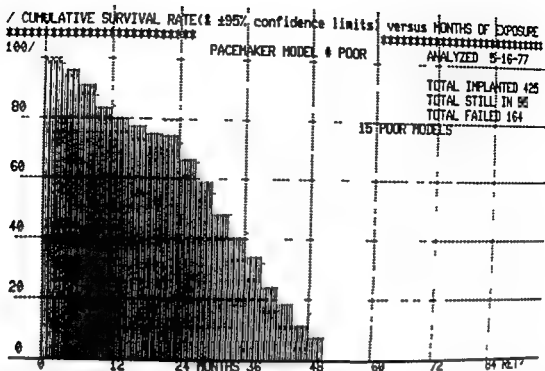


Fig 6 *Poor* = Failures begun during the first three months after implant. Cumulative survival falls very rapidly. There is 50 per cent survival 30 to 33 months after implant. All units have failed by the 51 to 54 month (Unretouched photograph from cathode ray tube screen)

al demonstrated 12 to 15 months after implant, over 90 per cent at 18 to 21 months, and over 80 per cent at the end of two years (Fig 4)

*Fair* Over 90 per cent cumulative survival at 12 to 15 months, or under 75 per cent at 18 to 21 months or under 50 per cent at the end of two years (Fig 5)

*Poor* Under 90 per cent survival at 12 to 15 months, or under 75 per cent at 18 to 21 months or under 50 per cent at the end of two years (Fig 6)

Two additional displays compare the long term 1969 to 1977 quality of all non nuclear models of two major manufacturers. As these two graphs include a long period of observation they are less affected by a single good or bad model and represent long range manufacturing performance (Fig 7, A and B). These data show that one manufacturer has provided substantially poorer quality over the past eight years. Obviously, the present situation is not clear from these data which clearly define the former situation.

#### Comparison of lithium and mercury-zinc power sources

Perhaps the most eagerly anticipated event in pacemaker technology is that of the change from a mercury-zinc power source to a lithium source. The first lithium pacemakers were implanted in

1973,<sup>1</sup> and a few have, consequently, reached the fourth year of use. Comparison of the longevity of all of the mercury-zinc and lithium units rapidly reveals the distinctly better behavior of the lithium and the statistically significant difference of the two power sources (Fig 8).

Another technical change, from discrete component design to hybrid circuitry, has been accompanied by a number of early failures. Analysis of the longevity of hybrid and discrete pulse generators of one manufacture with the same (mercury-zinc) power source indicates very well the early failure rate with both and that with the overlap of standard error the two were identical until the thirty fourth month of use, then the superiority of the hybrid circuitry becomes distinct, only to be lost in statistical insignificance during the fiftieth month after implant (Fig 9).

Equally the rate of current drain from a mercury-zinc battery has been thought to be a significant factor in the longevity of the pulse generator: the slower the drain the longer the life. Two groups of generators have been compared: one with a fixed and relatively high current drain, the second with a variable and as used a very low output. The effect of low current drain becomes immediately apparent with a statistically significant difference between the

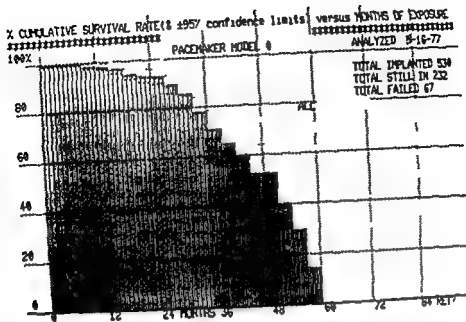


Fig 7 A and B Comparison of two pacemaker manufacturers. Note that in one manufacturer (A) 2 per cent of units failed during the first year the 50 per cent survival time was during the 51 to 64 months and the last failure occurred after the 117th month. In the other (B) only 92 per cent survival exists at one year the 50 per cent survival was during the 36 to 48th month after implant and the last failures occurred during 57 to 60th months after implant. (Photographs from cathode ray tube screen. Identification deleted)

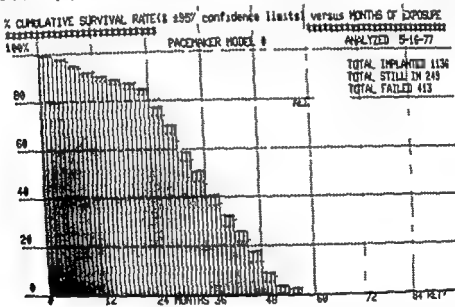


Fig 7B For legend see preceding page

two at the thirty-sixth month following implant. The lower drain is clearly associated with prolonged longevity (Fig 10)

#### Patient longevity

The longevity of patients following pacemaker implant is of course a function of factors unique

to each patient and each disease process. Nevertheless as for the calculation of the life table for the general population and for patients with other disease processes the longevity calculations using the life table technique are valuable.

The pacemaker population survival can be



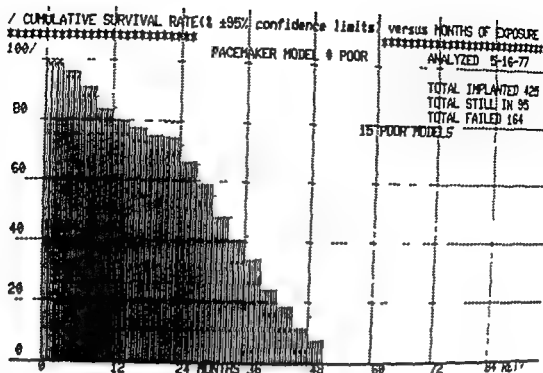


Fig 6 Poor = Failures begin during the first three months after implant. Cumulative survival falls very rapidly. There is 80 per cent survival 30 to 33 months after implant. All units have failed by the 51 to 54 month (Unretouched photograph from cathode ray tube screen.)

al demonstrated 12 to 15 months after implant, over 90 per cent at 18 to 21 months and over 80 per cent at the end of two years (Fig 4)

*Fair* Over 90 per cent cumulative survival at 12 to 15 months, or under 75 per cent at 18 to 21 months or under 50 per cent at the end of two years (Fig 5)

*Poor* Under 90 per cent survival at 12 to 15 months, or under 75 per cent at 18 to 21 months, or under 50 per cent at the end of two years (Fig 6)

Two additional displays compare the long term 1969 to 1977 quality of all non nuclear models of two major manufacturers. As these two graphs include a long period of observation they are less affected by a single good or bad model and represent long range manufacturing performance (Fig 7, A and B). These data show that one manufacturer has provided substantially poorer quality over the past eight years. Obviously, the present situation is not clear from these data, which clearly define the former situation.

#### Comparison of lithium and mercury-zinc power sources

Perhaps the most eagerly anticipated event in pacemaker technology is that of the change from a mercury-zinc power source to a lithium source. The first lithium pacemakers were implanted in

1973<sup>1</sup> and a few have, consequently, reached the fourth year of use. Comparison of the longevity of all of the mercury-zinc and lithium units rapidly reveals the distinctly better behavior of the lithium and the statistically significant difference of the two power sources (Fig 8).

Another technical change from discrete component design to hybrid circuitry, has been accompanied by a number of early failures. Analysis of the longevity of hybrid and discrete pulse generators of one manufacture with the same (mercury-zinc) power source indicates very well the early failure rate with both and that with the overlap of standard error the two were identical until the thirty fourth month of use, then the superiority of the hybrid circuitry becomes distinct, only to be lost in statistical insignificance during the fiftieth month after implant (Fig 9).

Equally, the rate of current drain from a mercury-zinc battery has been thought to be a significant factor in the longevity of the pulse generator, the slower the drain the longer the life. Two groups of generators have been compared one with a fixed and relatively high current drain, the second with a variable and as used a very low output. The effect of low current drain becomes immediately apparent with a statistically significant difference between the

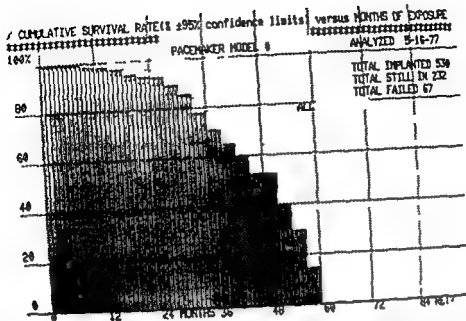


Fig. 7 A and B Comparison of two pacemaker manufacturers. Note that in one manufacturer (A) 2 per cent of units failed during the first year, the 50 per cent survival time was during the 51 to 54 months and the last failure occurred after the sixtieth month. In the other (B) only 9 per cent survival exists at one year, the 50 per cent survival was during the 36 to 39th month after implant, and the last failure occurred during 57 to 60th months after implant. (Photographs from cathode ray tube screen. Identification deleted.)

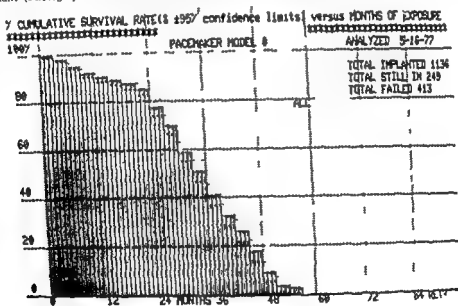


Fig. 7B For legend see preceding page

two at the thirty sixth month following implant. The lower drain is clearly associated with prolonged longevity (Fig. 10).

#### Patient longevity

The longevity of patients following pacemaker implant is of course a function of factors unique

to each patient and each disease process. Nevertheless, as for the calculation of the life table for the general population and for patients with other disease processes, the longevity calculations using the life table technique are valuable.

The pacemaker population survival can be

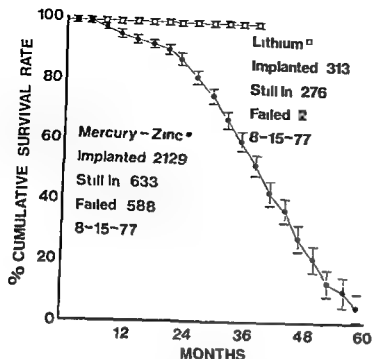


Fig 8 A comparison of the longevity of all mercury-zinc pacemakers used since 1969 and of lithium units used since 1974

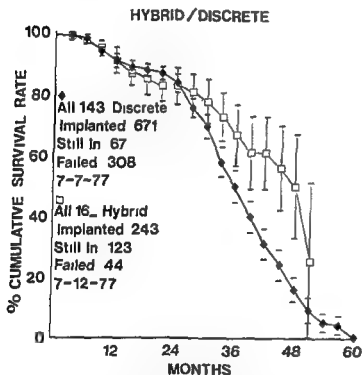


Fig 9 Comparison of hybrid and discrete circuits from a single manufacturer both using mercury-zinc batteries. Note little change in survival with the newer circuitry though a significant improvement does exist between the 33 and 51 months

calculated for a variety of segments. Implantation of pacemakers is readily calculable since 1962. Calculations have been made over a period of 14 years to the end of 1976 and several different approaches have been used.

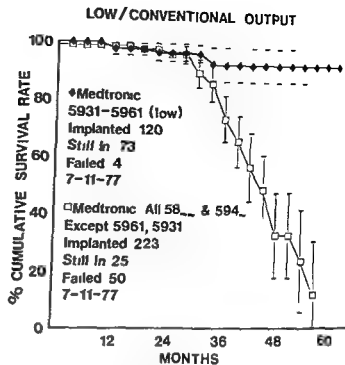


Fig 10 The benefits of reduced battery drain. Both series are from the same manufacturer both with mercury-zinc batteries. A significant difference in survival occurs at the 36th month following which the difference in survival patterns becomes progressively more pronounced.

The simplest analysis is that of the proportion of patients implanted by decade of age at implant and then further subdivided into male and female. This analysis shows that 40 per cent of all patients with pacemakers are initially implanted between the age of 70 to 80 years; that age 60 to 70 accounts for about 21 per cent and age 80 to 90 for 25 to 30 per cent; that 3.8 per cent are under 50 years of age and that 2.6 per cent are over 90 years of age and that at each age more men are implanted than women (Fig 11).

This disparity of men over women is then confirmed by the calculation of the implant percentage with men and women weighted to their representation in the population. Each pair of bars represents the percentage of each sex implanted of the total at that age group and corrected for the proportion in the population (Fig 12).

Patient survival can be compared to the survival of the general population in the USA. As a broad representation of over 90 per cent of all patients (only those under 65 years of age were eliminated) comparisons were made to population longevity at 70 years and 76 years. Comparison of patients of 65 to 75 with that of the general population at age 70 indicates an almost identical

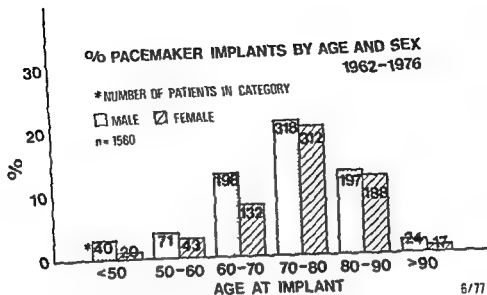


Fig 11 The ratio of pacer implants by age and sex. A plurality of patients is between 70 and 80 years of age.

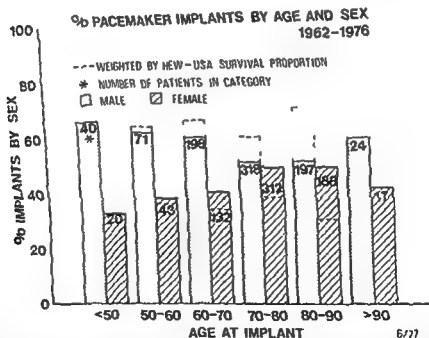


Fig 12 The ratio of pacer implants by age and sex weighted by the ratio of men to women during each age group. As there are more women than men at each age group, the actual incidence of arrhythmias requiring pacer implant is greater for men during each period.

survival to the eleventh year when statistical significance ceases.

The older patient group i.e. all those 75 to 100 years at implant have a significantly superior survival compared to age 76 for the general

population after the fifth year following implant (Fig 13).

Calculation of patient survival by age groups and the survival of the full group (from 0 to 100 years) displays the survival of the entire popula-

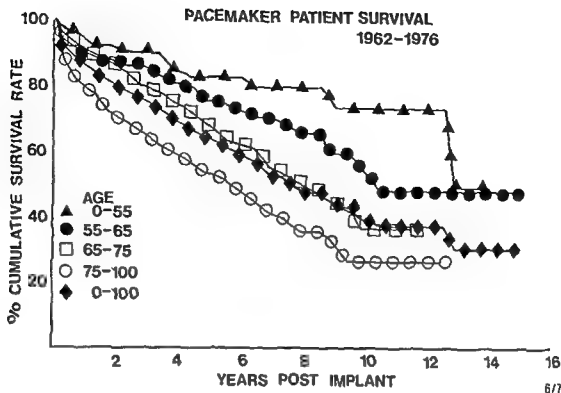


Fig 13 Patient survival by various age groups. As may be expected the younger the patient the more favorable the outlook

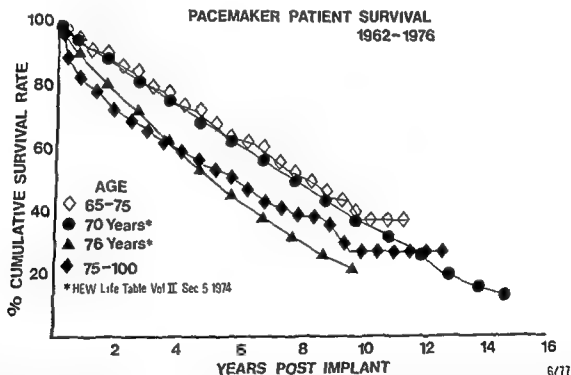


Fig 14 Patient survival compared to the life expectancy in the U S A. Pacer patients have the life expectancy of the general population and there is a suggestion (though not statistically significant) that survival may be even better

tion of pacemaker patients and of each population segment. The data, as expected, show the youngest patients with the greatest survival with each succeeding older group with a lessened survival (Fig 14).

Many more displays are possible i.e. for men compared to women at all ages for specific arrhythmias for all patients as a function of intercurrent disease etc. Obviously these data are invaluable for selection of appropriate hardware.

to be implanted and for planning for health services and insurance costs

At the present time patient needs require the maintenance of data concerning the operation of prosthetic devices. Clinic operation requires hard data concerning longevity and failure patterns to determine follow up patterns. Regulatory agencies require that data to be aware of the actual state of the art. Manufacturers need it to evaluate their efforts and third party insurers require it to calculate cost projections. Only a computer based carefully maintained statistical survey can provide that information.

#### REFERENCES

- 1 Green C D, Forbes W, Bain W H, Shaw G B and Kenmore A C F. Pacemaker lifetimes: a review and definitions based on experience in Glasgow with Chardack-Greathatch (Medtronic) pacemakers. *Am HEART J* 80:414 1970
- 2 Schalldig A and Lammertmann M. Comparison of function time of different pacemaker systems. *Ann Cardiol Aniol* 20:367 1971
- 3 Welts J J, Bonnet M, Stoltz J P, Kevorkian M, Proger G and Fontaine G. Durée et panne des pacemakers. *Arch Mal Coeur* 65 1977 1972
- 4 Parsonnet V, Myers G H, Giffert L, and Zucker I R. Prediction of impending pacemaker failure in a pacemaker clinic. *Am J Cardiol* 25:311 1978
- 5 Furman S, Escher D J W, Parker II and Solomon N. Electronic analysis for pacemaker failure. *Ann Thorac Surg* 8:57 1969
- 6 Morse D P, Tesler U F, and Lemola G M. The actual lifespan of pacemakers. *Chest* 64:454 1973
- 7 Grunkemeier G L, Dobbs J L, and Starr A. Statistical analysis of pacemaker follow up data. *Circulation* 53:241 1976
- 8 Cutler S J and Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis* 8:699 1958
- 9 Anderson H P, Bonchek L J, Grunkemeier G L, Lambert L E, and Starr A. The analysis and presentation of surgical results by actuarial methods. *J Surg Res* 16:274 1974
- 10 Greathatch W. The statistical reliability of lithium ion diode batteries in Advances in pacemaker technology. Schaldach, M and Furman S. eds. New York/Heidelberg 1975. Springer Verlag p 340
- 11 AAMI Pacemaker Standard. August 1975. FDA Contract No 27374-5083
- 12 Lillehei, H C, Romero L, H Beckman C B, Burroughs, J and Friedberg H D. A new solid state long life lithium powered pulse generator. *Ann Thorac Surg* 18:479 1974

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore, all manuscripts must be accompanied by the following statement signed by each author:

The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original and is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

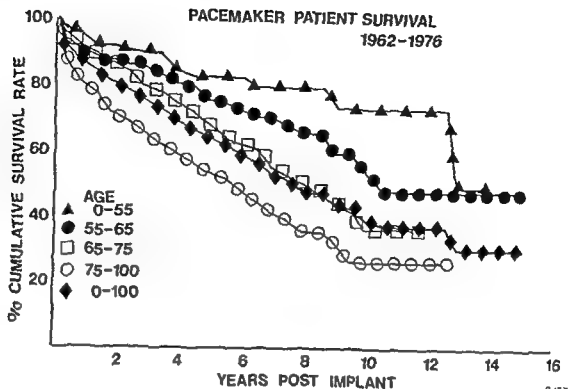


Fig 13 Patient survival by various age groups. As may be expected, the younger the patient the more favorable the outlook.

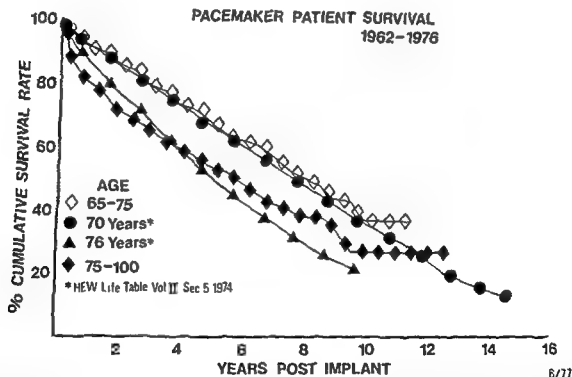


Fig 14 Patient survival compared to the life expectancy in the U.S.A. Pacer patients have the life expectancy of the general population and there is a suggestion (though not statistically significant) that survival may be even better.

tion of pacemaker patients and of each population segment. The data, as expected, show the youngest patients with the greatest survival, with each succeeding older group with a lessened survival (Fig 14).

Many more displays are possible i.e., for men compared to women at all ages for specific arrhythmias for all patients as a function of intercurrent disease etc. Obviously these data are invaluable for selection of appropriate hardware.

from chronic ischemia due to the underdeveloped blood supply

Rheumatic valvulitis has occurred in seven cases of single coronary artery. In our patient the rheumatic etiology is supported by diffuse thickening of both mitral cusps at the time of surgery and by the presence of microscopic fibrosis. The association of rheumatic valvulitis with myocardial infarction in our patient was apparently fortuitous. Nevertheless the combination of chronic mitral regurgitation perhaps made worse by a ruptured chorda and left ventricular dysfunction from the myocardial infarction led to congestive heart failure in this patient.

In summary myocardial infarction in single coronary artery is quite unusual and may be due to underdeveloped blood supply with secondary fibrosis.

Murray C Newton Jr MD

Laurence R Burnett MD

Cardiology Division

University of Virginia School of Medicine

Charlottesville Va 22901

## REFERENCES

- 1 Alexander R W and Griffith C C Anomalies of the coronary arteries and their clinical significance. *Circulation* 24:800 1959
- 2 Oden J A Congenital anomalies of the coronary arteries. *Am J Cardiol* 25:474 1970
- 3 Hillestad L and Eie H Single coronary artery. *Acta Med Scand* 189:409 1971
- 4 Robert J T and Loobe S H Congenital single coronary artery in man. *Am Heart J* 34:187 1947
- 5 Ogden J A and Goodyer A V N Patterns of distribution of the single coronary artery. *Yale J Biol Med* 25:11 1970
- 6 Spring D A and Thomson J R Severe atherosclerosis in the single coronary artery. *Am J Cardiol* 31:67 1973
- 7 Halpern I C Penny J L and Kennedy R J Single coronary artery. *Am J Cardiol* 19:474 1967
- 8 Tomary A and Reid J D Single coronary artery with myocardial infarction and AV block. *Arch Pathol* 99:143 1973
- 9 Shattough M D and White M S Single coronary artery: analysis of the anatomic variation, clinical importance and report of five cases. *JA MA* 230:743 1974
- 10 Fortum J J and Roberts W C Congenital atresia of the main left coronary artery. *Am J Med* 50:343 1971
- 11 Krumpholtz F B and Ehrlich W F Varieties of single coronary artery in man occurring as isolated cardiac anomalies. *Am J Med Sci* 196:407 1938
- 12 Dent E D and Fisher R S Single coronary artery: report of two cases. *Ann Intern Med* 44:1074 1956
- 13 Swan P and Fitzpatrick M Single coronary artery. *Br Heart J* 36:457 1974
- 14 Tremouretoux J, Brasseur L, Meersseman F and Vavenne F Infarctus myocardique auriculaire et ventriculaire dans un Cas de Coronaire Unique. *Acta Cardiol* 14:425 1959
- 15 Allen G L and Snider T H Myocardial infarction with a single coronary artery. *Arch Intern Med* 117:61 1967
- 16 Smith J C Review of single coronary artery with report of two cases. *Circulation* 1:1168 1950
- 17 Davis L P and Compton V Congenital absence of the left coronary artery. *Med Times* 90:293 1968
- 18 Chapman D W and Peterson P H Unusual forms of coronary disease as demonstrated by percutaneous coronary angiography. *Med Rec Annals (Houston)* 67:370 1964
- 19 Chaitman B R, Leperance J, Salmel J and Bourassa M G Clinical angiographic and hemodynamic findings in patient with anomalous origin of the coronary arteries. *Circulation* 53:199 1976
- 20 Pachinger O M, Vanden Hoven P and Judkins M J Single coronary artery—A cause of angina pectoris. *Eur J Cardiol* 2/2:161 1974

## Of plastic materials in clinical medicine

The trend toward greater use of plastic materials in clinical practice has advantages and disadvantages. The convenience and advantage of discarding plastic devices after use and the assurance of individual use are definite. The lack of need to clean and sterilize these materials is a definite cost advantage. However, there are at least two plastic devices that are important and frequently used in hospitals which are certainly traumatizing and injurious to patients: namely the plastic needle and the plastic nasogastric tube. Both are traumatizing, especially the plastic nasogastric tube. This tube is so rigid and inflexible that it produces pressure necrosis at every turn it makes on its course from the nares to the stomach. Even worse, its leading edge is often so sharp and so rigid that it scrapes and tears the surfaces of the nasopharynx as it is passed into the stomach, especially in the unconscious patient. The resultant hemorrhage can be large, and the blood is aspirated into the respiratory tract which leads to complication associated with choking and the development of aspiration pneumonia. In a recent instance at a local hospital

an area of pressure necrosis in a patient bled so profusely that the patient became exsanguinated as he quietly lay in his bed asleep during the night. He was found dead in bed early the next morning. There is available the much tested and superior soft Levine rubber nasogastric tube. Why not use it? It is a simple and extremely useful and important clinical device but unfortunately some physicians do not know how to use any nasogastric tube.

There is a need to learn more about the advantages and disadvantages of plastic clinical devices. The devices are all extremely useful and necessary in the practice of medicine but who buys plastic devices and why? We are overly committed to plastics for insufficient reasons. Some plastic things are good but many are bad. At least let's not use those that hurt our patients.

G F Burch MD  
Tulane University School of Medicine  
and Charity Hospital of Louisiana  
New Orleans, La



## Single coronary artery with myocardial infarction and mitral regurgitation

Single coronary artery without other congenital cardiac defects has been thought an interesting but unimportant finding because its peripheral distribution is usually adequate for myocardial needs. We studied a patient with single coronary artery myocardial infarction and mitral regurgitation.

A 45 year old man entered the hospital for congestive heart failure with mitral regurgitation. The electrocardiogram and vectorcardiogram showed an old anterior myocardial infarction and atrial fibrillation. Cardiac catheterization revealed severe mitral regurgitation with mild pulmonary hypertension. Selective coronary angiography showed the right coronary artery to be a large dominant vessel (Figs 1 and 2). Almost immediately after its origin a large branch arose which represented the left coronary artery. It coursed posterior to the aorta and divided into a marginal circumflex artery, a very small left anterior descending and several diagonal branches which followed the usual distribution (R 2 A in Ogden's classification). No athero-sclerosis was seen. At surgery, the left anterior descending artery was hypoplastic. A ruptured chorda tendineae of the anterior mitral leaflet was found. The diffusely thickened mitral valve was replaced by a porcine xenograft. Microscopic examination revealed focal vascularization consistent with rheumatic valvulitis.

Anomalies of the coronary arteries occur in 2.85 per 1000 autopsies. A large series of coronary angiograms yielded an incidence of 1.9 per 1000 studies. Single coronary artery comprises 4.5 per cent of congenital coronary anomalies. The number of reported cases has greatly increased with the widespread use of coronary angiograms. Myocardial infarction has occurred in 22 cases.

Of these 15 were male and five were female with an average age of 53 years. Fifteen of 22 (73 per cent) patients with infarction had a single vessel originating from the right sinus which is unusual since single coronary arteries generally originate equally from the right and left sinuses of Valsalva. Angina pectoris with ischemic ST segment depression may occur with a single coronary artery in the absence of atheromatous obstruction. Furthermore, atrial pacing and measurement of coronary arteriovenous lactate differences have shown ischemic ST segment depression and lactate production in this situation. Moreover, focal myocardial necrosis and fibrosis may be associated with clinical and electrocardiographic evidence of severe myocardial infarction without atheromatous occlusion of coronary arteries when a portion of the myocardium is supplied by a small or hypoplastic vessel.

The absence in our patient of atheromatous obstruction in the coronary artery with evidence of myocardial infarction by electrocardiogram, vectorcardiogram and left ventriculography led us to conclude that myocardial fibrosis occurred

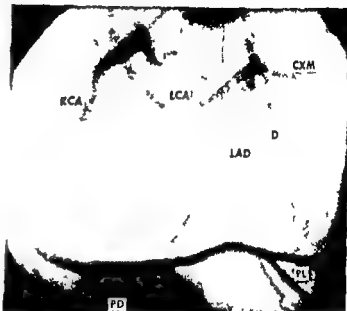


Fig 1 Selective injection of the right coronary artery in the 30 degree left anterior oblique projection. RCA = right coronary artery. LCA = left coronary artery. LAD = left anterior descending. D = diagonal. CxM = circumflex marginal. PD = posterior descending. PL = posterolateral branches.

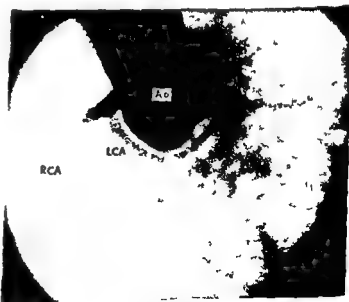


Fig 2 Aortic supra-valvular injection in the 30 degree left anterior oblique projection. Ao = aorta. RCA = right coronary artery. LCA = left coronary artery.

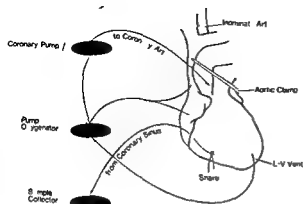


Fig 2 Cardiopulmonary bypass was carried out as in the diagram above. Coronary perfusion was maintained through a separate calibrated pump and cannulation of the clamped aortic root. A catheter can be seen lying in the coronary sinus for collection of coronary sinus blood and a snare placed around the coronary sinus to assure total blood collection (Reproduced from Engelman R M Chandra R Baumann F G and Goldman R A Myocardial reperfusion a cause of ischemic injury during cardiopulmonary bypass Surgery 80:266 19 6)

subepicardial flow decreased significantly ( $p < 0.05$ ) from  $1.10 \pm 0.03$  to  $0.69 \pm 0.08$ . It is apparent that the myocardial tissue most susceptible to ischemic injury secondary to edema formation during bypass is the subendocardial layers, a fact long suspected by cardiac surgeons who see subendocardial ischemia clinically. The degree of decrease in subendocardial perfusion is especially profound because the normal protective reactive hyperemic response of the coronary bed following ischemia is abolished by this edema formation. In the same series of animals the coronary vascular resistance before ischemia was  $0.30 \pm 0.07$ . This increased after three ischemic periods to  $0.34 \pm 0.04$ . A normal response would be for the resistance to significantly decrease as was noted after the first of the three ischemic periods (Table 1).

The development of intraoperative myocardial edema is a serious complication of cardiopulmonary bypass to be avoided whenever possible. The means at our disposal include (1) avoidance of entricular fibrillation (2) restriction of ischemic time and provision for longer reperfusion periods (3) use of cardioplegic hypothermic protection during ischemic arrest (4) avoidance of overperfusion of the myocardium after ischemia by not using a high perfusion pressure and (5) utilization of mannitol or other hyperosmolar perfusate to reduce postischemic edema formation. The use of one or more of these modalities has sharply reduced the risk of ischemic injury during intracardiac surgical procedures to one to two per cent in most centers.

Richard M Engelman, M.D.  
Department of Surgery  
University of Illinois  
Abraham Lincoln School  
of Medicine  
Chicago, ILL 60612

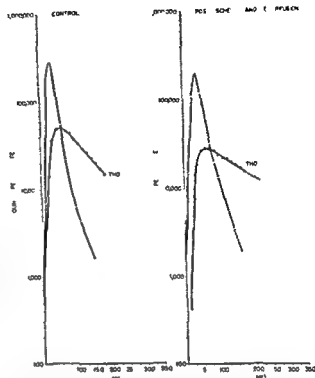


Fig 3 An example of the plotted semilog time-concentration curves demonstrates the results obtained between control and post ischemic studies (Reproduced from Engelman R M, Chandra R Baumann F G and Goldman R A Myocardial reperfusion a cause of ischemic injury during cardiopulmonary bypass Surgery 80:266 19 6)

Table 1 Coronary vascular resistance

| Time period<br>(minutes of arrest) | mm Hg/mL<br>/min/100 Gm |
|------------------------------------|-------------------------|
| Control                            | $0.30 \pm 0.07$         |
| 30                                 | $0.20 \pm 0.04$         |
| 60                                 | $0.26 \pm 0.03$         |
| 90                                 | $0.34 \pm 0.04$         |

#### REFERENCES

- West P N, Connors J H, Clark R E, Roberts R, Sobel B H, Williamson J R, and Weldon C S. Functional impairment of the microcirculation in ischemic myocardium. *Ann Thorac Surg* (In press).
- Powell W J Jr, Flores J, DiBona D M, Flores J, Frega N, and Leaf A. Effects of hyperosmotic mannitol in reducing ischemic cell swelling and minimizing myocardial necrosis. *Circulation* (Suppl 1) 53:145 1976.
- Powell W J Jr, Flores J, DiBona D M, and Leaf A. The role of cell swelling in myocardial ischemia and the protective effect of hypertonic mannitol. *J Clin Invest* 52:66a 1973.
- Engelman R M, Chandra R, Baumann F G, and Goldman R A. Myocardial reperfusion a cause of

## Myocardial edema, a complication of ischemic arrest during cardiopulmonary bypass

Ischemic arrest is frequently employed during cardiopulmonary bypass to allow the surgeon to operate upon a quiet bloodless flaccid heart for precise repair of cardiac defects or creation of a small anastomosis. The consequences of ischemia include degeneration of capillary endothelial cells<sup>1</sup> and the breakdown of the sodium pump located in the cell membrane. This active transport mechanism responsible for maintaining an intracellular-extracellular sodium gradient and counterbalancing the osmotic effect of high intracellular colloids stabilizes cell volume. With reduction of this transport mechanism due to a decrease in energy support sodium enters the cell and cell swelling occurs. With myocardial and capillary endothelial cell swelling and degeneration (Fig. 1) a diminution in perfusion occurs preventing nutrient flow from reversing the effects of ischemia despite reperfusion of the myocardial muscle mass. Ultimately with repeated ischemic insults considerable edema accumulates resulting in a measurable volume increase in myocardial extravascular water.

Using the technique of multiple indicator dilution curves as described by Ramsey and associates<sup>2</sup> for the lung myocardial extravascular water was measured in 11 pigs after three 30 minute periods of normothermic ischemic arrest interrupted by 5 minutes of perfusion at 100 mm Hg with the heart

fibrillating. The experimental model is shown in Fig. 2. Myocardial intravascular water was measured using 4 to 5  $\mu$ Ci of radioactive iodinated serum albumin (RISA) and total myocardial water using 50  $\mu$ Ci of tritiated water (THO). Both markers were simultaneously injected as a bolus into the coronary perfusate and all coronary sinus blood was retrieved in the timed sample collector. Coronary sinus blood counts per minute of RISA and THO were plotted on a log scale against a linear time scale in seconds (Fig. 3). The straight line extrapolation of the exponential descending limb calculated by computer enabled total flow for RISA and THO to be determined using standard formulas. The volume into which each indicator was distributed between injection and sampling sites was determined using the mean transit time calculation. The difference between RISA and THO volumes corresponds to an approximation of the extravascular water volume.

The determination of extravascular water in the heart of control pigs averaged  $46.4 \pm 1.7$  ml/100 Gm. This increased significantly ( $p < 0.05$ ) to  $52.6 \pm 2.0$  ml/100 Gm in postischemic hearts. Associated with the development of myocardial edema was a significant selective decrease in subendocardial perfusion as measured by radioactive microsphere distribution comparing preischemic (control) animals with those following ischemia. The perfusion ratio of subendocardial to



Fig. 1 An electronmicrograph of a heart after ischemia documents myofibrillar degeneration, enlarged edematous mitochondria (M) with broken disarranged cristae and a clear matrix to the point of vacuolization (V). Capillary endothelial cells show degenerated organelles and blebs protruding into the lumen (double arrows). Arrow = intercalated disc. (Original magnification  $\times 11,000$ ). (Reproduced from Engelmann R. M., Chandra R., Baumann F. G. and Goldman R. A.: Myocardial reperfusion: a cause of ischemic injury during cardiopulmonary bypass. *Surgery* 80:266, 1976).

naire shows that roughly half the country favors the 2 Gm sodium diet. This practice presumably derives from earlier data that demonstrated decreased renal blood flow in congestive heart failure with secondary retention of salt and water. This degree of sodium restriction may be dangerous for many reasons principally that in the presence of decreased cardiac output loss of extracellular sodium chloride may further decrease output. An argument can also be made against unlimited salt intake since some Americans habitually consume large amounts of salt with their meals and the risk of fluid overload and congestive heart failure in the presence of acute myocardial infarction is real. A reasonable compromise would appear to be a no added salt diet which in most hospitals contain 3 to 4 Gm of sodium with alterations made according to clinical status.

Over 90 per cent of institutions in our sample have no potassium restriction or supplementation in their CCU diets. This is probably due to an appreciation of the lability of serum potassium levels in situations of changing fluid status, acidosis, diuretic therapy, vomiting and the like with the need for frequent reassessment. Potassium liberalization would be helpful in the presence of hypokalemia commonly due to frequent diuretic use while potassium restriction would be appropriate where there is severe hyperkalemia or renal failure. No generalization about what constitutes optimal potassium intake is possible.

Should bulk be restricted in the Coronary Care Unit diet? Liquid diets may reduce the risk of cardiac arrest by avoidance of the spasmodic and arrhythmia producing effects of gasping or of straining during bowel movements. They may also reduce aspiration. On the other hand some patients find liquid or low bulk diets constipating and under these circumstances increased bulk may be more desirable. Again no universal recommendation regarding optimal bulk in the CCU diet can be made.

Lastly the topic of carbohydrate restriction was surveyed. Fully 80 per cent of institutions responding did not restrict carbohydrates in the Coronary Care Unit diet. We know of no data to support or refute this practice but since glucose has been shown to be an important fuel source for the acutely ischemic myocardium there seems to be no good reason to selectively limit carbohydrate intake in the CCU.

In conclusion we have demonstrated widely differing practices in Coronary Care Unit diet therapy in the United States. Caloric intake should be individualized and extremes such as overfeeding which may predispose the patient to angina or near-starvation diets which predispose to hypoglycemia are to be avoided. The diet should eliminate items likely to cause gastrointestinal intolerance in specific patients and be comfortably modified in bulk ideally with multiple small feedings. Both cholesterol and fat should probably be limited.

Optimal salt intake will vary but for uncomplicated cases a no added salt diet seems reasonable. Depending on circumstances, there may be benefit from increased or decreased dietary potassium.

Metabolic needs of the infarction patient must be assessed daily supplemented by regular determinations of clinical status, intake, output, serum glucose and electrolytes and by active consultation with the dietician. Perhaps most important, what is needed is more scientifically determined information about how dietary intake during acute myocardial infarction affects cardiac metabolism and the clinical course of the CCU patient.

■ E. Warren, Lt MC USNR  
J. S. Alpert, Lt Cdr MC USNR  
G. S. Francis, Lt Cdr MC USNR  
Cardiology Division  
Dept. of Internal Medicine  
Natal Regional Medical Center  
San Diego, Calif. 92134

## REFERENCES

1. Wenger N K, Hellerstein H K, Blackburn H and Castranova S J. Uncomplicated myocardial infarction. Current physician practice in patient management. *JAMA* 224:513, 1973.
2. Feldschuh J and Yucoglu Y Z. Study of daily caloric intake of patients in the coronary intensive care unit. *Anesthesiology* 26:334, 1975.
3. Ernstone A C and Altschule M D. The effect of insulin hypoglycemia on the circulation. *J Clin Invest* 10:571-574, 1931.
4. Friedberg C K. *Diseases of the Heart*, 3rd ed. Philadelphia 1965 W B Saunders Co pp 1661.
5. Blotner H. Coronary disease in diabetes mellitus. *N Engl J Med* 203:708, 1930.
6. Turner K H. Insulin shock as the cause of cardiac pain. *Am Heart J* 5:61, 1931.
7. Cohen I M, Alpert J S, Francis G M, Vieweg W V R, and Hagan A D. Safety of hot and cold liquids in patients with acute myocardial infarction. *Chest* 71:450, 1977.
8. Jones M. The way to a man's heart. *attack III Med J Aust* 1973 pp 170-174.
9. Goldberger E. Dangers of a low sodium diet in the treatment of acute myocardial infarction. *Am J Cardiol* 8:300, 1961.
10. Christakes S and Winston M. Nutritional therapy in acute myocardial infarction. *J Am Diet Assoc* 63:230, 1973.
11. Opie L H. Metabolic response during impending myocardial infarction. I. Relevance of studies of glucose and free fatty acid metabolism in animal. *Circulation* 45:483, 1972.

- ischemic injury during cardiopulmonary bypass *Surgery* 80 256 1976
- 5 Ramsey L H Puckett W Jose A and Lacy W W Pericapillary gas and water distribution volumes of the lung calculated from multiple indicator dilution curves *Circ Res* 15 275 1964
- 6 Buckberg G D Towers B Pagha D E Mulder D G and Maloney J V Subendocardial ischemia after cardiopulmonary bypass *J Thorac Cardiovasc Surg* 64 669 1972
- 7 Najafi H Lal R Khalil M Serry C Rogers A and Haklin M Left ventricular hemorrhagic necrosis *Ann Thorac Surg* 12 440 1971
- 8 Hottentrott C E Towers B Kurki H J Maloney J V Jr and Buckberg G The hazard of ventricular fibrillation in hypertrophied ventricles during cardiopulmonary bypass *J Thorac Cardiovasc Surg* 66 742 1973
- 9 Engelman R E Levitsky S and Wyndham Christopher R C Optimal conditions for reperfusion during cardiopulmonary bypass *Circulation* 56(Suppl 2) 145 1977
- 10 Gnepp R B Stinson E H Oyer P E Copeland J G and Shumway N E The superiority of aortic cross clamping with profound local hypothermia for myocardial protection during aorta-coronary bypass grafting *J Thorac Cardiovasc Surg* 70 995 1975
- 11 Nelson R L Fej K H Follette D M Lutes J J Deland E Maloney J V Jr and Buckberg G D The critical importance of intermittent infusion of cardioplegic solution during aortic cross-clamping *Surg Forum* 27 241 1976
- 12 Olinger G N Po J Maloney J V Jr Mulder D G and Buckberg G D Coronary revascularization in high versus low risk patients the role of myocardial protection *Ann Surg* 182 293 1975

## Diet in the Coronary Care Unit\*

Despite the fact that in 1970 a poll of 3 600 doctors revealed 90 per cent to favor some form of diet therapy for their CCU patients great confusion persists over what diet is best. We surveyed over 290 major medical centers using a questionnaire and asked chief dietitians if doctors used a routine CCU diet for the first 24 to 72 hours of admission. If the answer was negative they were asked to fill out the remainder of the questionnaire using the most common diet ordered in the setting of acute myocardial infarction. No distinction was made between the first eight to twenty four hours (where admittedly many patients receive nothing by mouth as their condition is stabilized) and the remaining 48 to 60 hours of the acute phase of coronary care.

### Results

Seventy one per cent of the 290 institutions polled responded. About 60 per cent of dietitians acknowledged the use of a routine CCU diet. Caloric intake was evenly distributed across a wide range of choices: less than 1 000 calories in 13 per cent of cases, 1 000 to 2 000 calories in 35 per cent, 2 000 to 1 400 in 20.5 per cent, 1 400 to 1 600 in 16 per cent, 1 600 to 2 000 in 20 per cent, greater than 2 000 calories per day in 5.5 per cent, and variable intake in 16.5 per cent. Only about half of these diets were bland. Most institutions clearly favor three meals per day (64 per cent) although significant numbers of patients (20.5 per cent) receive multiple small feedings or snacks. While the majority of diets restrict cholesterol or saturated fat (65 per cent) roughly 22 per cent of these restrict cholesterol only. Salt restriction in the form of a 2g Na diet was restricted in almost 50 per cent of cases although nearly 20 per cent of diets contain either no salt restriction or merely no added salt (about 4 Gm of sodium). Overwhelmingly CCU diets contain no potassium restriction. About half reduce roughage either via low bulk foods or

breads and relatively few (10 per cent) restrict carbohydrates.

From this data we may infer that no consensus exists regarding what to feed the CCU patient. In fact very little is known about the advantages and liabilities of different diets.

It has been shown that many myocardial infarction patients consume less than 200 calories a day in the CCU. Such starvation diets may result in profound hypoglycemia, a cause of increased cardiac work, angina, or myocardial necrosis. On the other hand, our data suggest that 40 per cent of hospitals feed their patients meals containing over 1 400 calories per day. Add to this at least 200 calories from "keep open" intravenous solutions of dextrose and water and it is apparent that many patients will arbitrarily be "overfed." This may at least theoretically be attended by angina due to increased cardiac output with splanchnic dilatation. Intuitively such problems might be lessened by the use of small frequent feedings although there has been no clinical study to support this.

Similarly the bland diet which our data shows to have wide acceptance has not been proved to have any special physiologic merit. In individual cases it may be prudent to restrict foods known to be tolerated poorly. Similarly cardiac stimulants are perhaps best avoided since they may increase heart rate and myocardial oxygen consumption. Hot and cold beverages however have been allowed with impunity without ill effects.

Most CCU diets restrict fat and cholesterol presumably because of the myocardial depressant effects of free fatty acids and the well known association of lipids and coronary artery disease. However it is curious that 22 per cent of diets contain restrictions in cholesterol only. It has been shown that the blood level of cholesterol is more susceptible to influence by the quantity and quality of fat in the diet than by the amount of cholesterol in it. Cholesterol absorption from the bowel is dependent upon dietary fat intake. Therefore it does not make sense to restrict cholesterol without concurrently restricting dietary fat, especially saturated fat.

How much salt should the CCU diet contain? Our question

\*The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

nature shows that roughly half the country favors the 2 Gm sodium diet. This practice presumably derives from earlier data that demonstrated decreased renal blood flow in congestive heart failure with secondary retention of salt and water. This degree of sodium restriction may be dangerous for many reasons, principally that in the presence of decreased cardiac output loss of extracellular sodium chloride may further decrease output. An argument can also be made against unlimited salt intake since some Americans habitually consume large amounts of salt with their meals and the risk of fluid overload and congestive heart failure in the presence of acute myocardial infarction is real. A reasonable compromise would appear to be a no added salt diet which in most hospitals contain 3 to 4 Gm of sodium with alterations made according to clinical status.

Over 90 per cent of institutions in our sample have no potassium restriction or supplementation in their CCU diets. This is probably due to an appreciation of the lability of serum potassium levels in situations of changing fluid status, acidosis, diuretic therapy, vomiting and the like with the need for frequent reassessment. Potassium liberalization would be helpful in the presence of hypokalemia commonly due to frequent diuretic use while potassium restriction would be appropriate where there is severe hyperkalemia or renal failure. No generalization about what constitutes optimal potassium intake is possible.

Should bulk be restricted in the Coronary Care Unit diet? Liquid diets may reduce the risk of cardiac arrest by avoidance of the vagovagal and arrhythmia producing effects of gasping or of straining during bowel movements. They may also reduce aspiration. On the other hand some patients find liquid or low bulk diets constipating and under these circumstances increased bulk may be more desirable. Again no universal recommendation regarding optimal bulk in the CCU diet can be made.

Lastly the topic of carbohydrate restriction was surveyed. Fully 80 per cent of institutions responding did not restrict carbohydrates in the Coronary Care Unit diet. We know of no data to support or refute this practice but since glucose has been shown to be an important fuel source for the acutely ischemic myocardium there seems to be no good reason to selectively limit carbohydrate intake in the CCU.

In conclusion we have demonstrated widely differing practices in Coronary Care Unit diet therapy in the United States. Caloric intake should be individualized and extremes such as overfeeding which may predispose the patient to angina or near starvation diets which predispose to hypoglycemia are to be avoided. The diet should eliminate items likely to cause gastrointestinal intolerance in specific patients and be comfortably modified in bulk ideally with multiple small feedings. Both cholesterol and fat should probably be limited.

Optimal salt intake will vary but for uncomplicated cases a no added salt diet seems reasonable. Depending on circumstances, there may be benefit from increased or decreased dietary potassium.

Metabolic needs of the infarction patient must be assessed daily supplemented by regular determinations of clinical status, intake, output, serum glucose and electrolytes and by active consultation with the dietitian. Perhaps most important, what is needed is more scientifically determined information about how dietary intake during acute myocardial infarction affects cardiac metabolism and the clinical course of the CCU patient.

S E Warren Lt MC USNR  
J S Alpert Lt Cdr MC USNR  
G S Francis Lt Cdr MC USNR  
Cardiology Division  
Dept of Internal Medicine  
Naval Regional Medical Center  
San Diego Calif 92134

#### REFERENCES

- 1 Wenger A K, Heflerstein H K, Blackburn H., and Castranova S J. Uncomplicated myocardial infarction. Current physician practice in patient management. *JAMA* 224:513-517.
- 2 Feldschuh J and Yuceoglu Y Z. Study of daily caloric intake of patients in the coronary intensive care unit. *Angiology* 26:334-339.
- 3 Ernst A C and Altchule M H. The effect of insulin hypoglycemia on the circulation. *J Clin Invest* 10:157-193.
- 4 Friedberg C H. Diseases of the Heart 3rd ed. Philadelphia 1966 W B Saunders Co pp 1681.
- 5 Blotner H. Coronary disease in diabetes mellitus. *N Engl J Med* 203: 99-100.
- 6 Turner A H. Insulin shock as the cause of cardiac pain. *AM HEART J* 5:671-1931.
- 7 Cohen I M, Alpert J S, Francis G S, Vieweg W V R and Hagan A D. Safety of hot and cold liquids in patients with acute myocardial infarction. *Chest* 71:450-1971.
- 8 Jones R. The way to a man's heart attack. *Med J Aug* 1973 pp 170-176.
- 9 Goldberger E. Dangers of a low sodium diet in the treatment of acute myocardial infarction. *Am J Cardiol* 8:300-1961.
- 10 Christakes C and Winston M. Nutritional therapy in acute myocardial infarction. *J Am Diet Assoc* 63:230-1973.
- 11 Opie L H. Metabolic response during impending myocardial infarction. I. Relevance of studies of glucose and free fatty acid metabolism in animals. *Circulation* 45:483-1972.

## Effect of vagus nerve stimulation on ventricular fibrillation threshold

To the Editor

We read with interest the article of Yoon and associates. Effects of vagal stimulation atropine and propranolol on fibrillation threshold of normal and ischemic ventricles in the January 1977 issue of AMERICAN HEART JOURNAL. Their findings further confirm observations made in our own laboratory to the effect that efferent vagal nerve stimulation (VNS) requires a background of augmented sympathetic tone in order to raise ventricular fibrillation threshold (VFT). We have noted as do Yoon and co-workers that vagal effects on ventricular vulnerability are annulled by pretreatment with propranolol. This is also the case with vagal effects on ventricular excitability.

Yoon and associates' conclusion that VNS raises VFT under control conditions while in agreement with the observations of Kent and colleagues is at variance with our own findings which are that VNS has little or no effect on VFT in the absence of augmented sympathetic tone. We employed a single pulse technique for VFT testing whereas Yoon and co-workers employed a train of pulses technique. It has been demonstrated that a train of closely spaced pulses delivered to the ventricles is a potent stimulus for local sympathetic neurohormonal release. We hypothesize that artifactual enhancement of sympathetic tone by the train of pulses technique explains the discrepancy between our results and those of Yoon and associates and Kent and colleagues. The important unifying observation is that the effect of VNS on VFT is mediated indirectly through cancellation of the effects of efferent adrenergic tone. Also the train of pulses technique may be unsuitable for VFT testing in circumstances in which a constant baseline level of sympathetic tone is desirable.

Burt S. Kolman M.D.  
Richard L. Verner Ph.D.  
Bernard Loun M.D.  
Cardiovascular Laboratories  
Department of Nutrition  
Harvard School of Public Health  
Boston, Massachusetts

## REFERENCES

1. Yoon M S, Han J, Tse W W, and Rogers R. Effect of vagal stimulation atropine and propranolol on fibrillation threshold of normal and ischemic ventricles. *Am Heart J* 93:60 1977.
2. Kolman B S, Verner R L, and Loun B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle. Role of sympathetic parasympathetic interactions. *Circulation* 52:578 1975.
3. Rabinowitz S H, Verner R L, and Loun B. Muscarinic effects of vagosympathetic trunk stimulation on the repetitive extrasystole (RE) threshold. *Circulation* 53:622 1976.
4. Verner R L, Rabinowitz S H, and Loun B. Vagal and adrenergic interactions and ventricular electrical stability. *Clin Res* 23:212A 1975.
5. Matta R J, Verner R L, and Loun B. Repetitive

extrasystole as an index of vulnerability to ventricular fibrillation. *Am J Physiol* 230:1469 1976.

6. Loun B and Verner R L. Neural activity and ventricular fibrillation. *N Engl J Med* 294:1160 1976.
7. Kolman B S, Verner R L, and Loun B. The effect of vagus nerve stimulation upon excitability of the canine ventricle. Role of sympathetic parasympathetic interactions. *Am J Cardiol* 37:1041 1976.
8. Kent K M, Smith E R, Redwood D R, and Epstein S E. Electrical stability of acutely ischemic myocardium. Influences of heart rate and vagal stimulation. *Circulation* 47:291 1973.
9. Vincenzi F and West T C. Release of autonomic mediators in cardiac tissue by direct subthreshold stimulation. *J Pharmacol Exp Ther* 141:185 1963.
10. Brady A J, Abbott B C, and Mommaerts W F H M. Inotropic effects of trains of impulses applied during the contraction of cardiac muscle. *J Gen Physiol* 44:415 1960.

## Reply

To the Editor

We appreciate the opportunity of responding to the letter of Dr. Kolman and colleagues. It is true that our findings confirm their observation that the effect of vagal stimulation on ventricular fibrillation threshold (VFT) is indirect and mediated through inhibition of the sympathetic activity. They indicate that our observation that vagal stimulation increases VFT in nonischemic ventricles is at variance with their results but the two results in open chest dogs are quite similar. They showed the mean increase in VFT of 26 per cent in 10 open chest dogs and we demonstrated the 35 per cent increase in eight open chest dogs. They decentralized the left stellate ganglion and employed a single pulse technique for VFT testing, while we left the stellate ganglia intact and used a train of rapid pulses for VFT determination. It is possible that the level of underlying sympathetic tone was higher in our dogs and this resulted in a greater increase in VFT during vagal stimulation. Their letter and our reply merely point out that the results of vagal stimulation on VFT can vary with different experimental techniques.

We also studied the effect of vagal stimulation in the eight dogs during acute coronary occlusion and found that vagal stimulation has no effect on VFT in ischemic ventricles. Myocardial ischemia produces marked depression in excitability and conductivity in the affected area leading to increased ventricular inhomogeneity and instability which facilitate ventricular arrhythmias. We concluded that the potentially beneficial effect of vagal stimulation was not strong enough to counteract the deleterious effects of myocardial ischemia and failed to increase VFT. In a recent clinical study, continuous infusion of a vagotonic agent, edrophonium hydrochloride, failed to alter the overall incidence of ventricular arrhythmias in patients with acute myocardial infarction. The frequency of ventricular premature beats was not significantly reduced and the appearance of ventricular tachyarrhythmias was not prevented by edrophonium infusion. Therefore

evidence is not yet available to indicate that vagotonic agents are useful in the management of patients with ventricular arrhythmias during acute myocardial infarction

Jack Han MD PhD  
 Myung S Yoon MD  
 Dept of Medicine (Cardiology)  
 Albany Medical College  
 Albany NY

# REFERENCES

- 1 Yoon M S Han J Tse W W and Rogers R Effects of vagal stimulation atropine and propranolol on fibrillation threshold of normal and ischemic ventricles AM HEART J 93 60 1977
- 2 Holman B S Verner R L and Lown B The effect of vagus nerve stimulation upon vulnerability of the canine ventricle Role of sympathetic parasympathetic interactions Circulation 52 578 1975
- 3 Miller R R Olson H G Vera Z DeMara A N Amsterdam E A and Mason D T Clinical evaluation of the enhancement of vagal tone in acute myocardial infarction by edrophonium hydrochloride Effects on ventricular arrhythmias His bundle electrography and left ventricular function AM HEART J 93 272 1977

## Wolff Parkinson White (Type B) Ebstein's anomaly and congenital ichthyosis

### To The Editor

I had the occasion to examine a 14 year-old white male with Wolff Parkinson White (Type B) Ebstein's anomaly and congenital ichthyosis. A family tree for four generations was constructed.

There are two siblings in his immediate family both are male and both have congenital ichthyosis. The family physician in rural Kentucky reports neither a cardiac murmur or a history of tachycardia. Electrocardiograms of the two brothers read by the author are normal.

A paternal uncle and the paternal grandmother also have this skin malady. The same physician reports no cardiac abnormalities in these individuals. Again I have read the grandmother's electrocardiogram and it is normal. None could be obtained on the uncle.

The other member of the family with congenital ichthyosis is a maternal great uncle. The family knew of no cardiac problems in this individual but objective first hand evidence is unavailable.

My review of the cardiology and dermatology literature did not reveal a previous observation of this triad.

Morris M Weiss MD FACC FACP  
 Associate Clinical Professor of Medicine  
 University of Louisville School of Medicine  
 Co Director Heart Station Jewish Hospital  
 Louisville Kentucky

# REFERENCES

- 1 Esterly M B The ichthyosiform dermatoses Pediatrics 42 990 1968
- Scheibler S L Adams P Jr and Anderson R C The Wolff Parkinson White syndrome in infants and children, Pediatrics 24 585 1959

- 3 James T N The Wolff Parkinson White Syndrome Ann Intern Med 71 389 1969
- 4 Shayder U W Inherited ichthyosis Arch Dermatol 102 10 19 0

## Venture research

### To the Editor

Your editorial in the December 1978 issue of AMERICAN HEART JOURNAL advocates revision of the present practice of allocating research grants. While agreeing with most of the sentiments expressed in the article, may I voice my disagreement on some points?

We all agree that the greatest asset of any country lies in the skills and talents of its people and it would serve the best interest of the country and of humanity if those possessing exceptional abilities, capable of original thought and holding the promise of great achievements were given every help and encouragement. The question is how these people are to be found and what is the best way of helping and encouraging them.

Unfortunately there is no known method of recognizing outstanding talent until its manifestation in outstanding achievement. Bright young people more often shine by virtue of a retentive memory and personal charm than by original thought. Conversely, men who later reveal themselves as geniuses, often seem to have difficulties in communicating with their fellows. Their work has often been overlooked and sometimes ridiculed by their contemporaries after its completion and publication. How can it be expected that a small panel of critics would recognize its merits in its incipient stage?

Apart from the difficulty of finding the geniuses of the future, the question still remains: what is the best way of fostering their talents? I strongly disagree with the opinion that society has to cross their palms with silver and pave their path with gold. Surely a sense of mission, the desire to leave the world a better place than they had found it, and the necessity of answering the question—if to no one else then to themselves—What have you done with your talents? must be a stronger incentive than wanting a bigger automobile than their neighbor.

Removing all obstacles and smoothing all paths does not seem to pay in the case of much lesser talents either, or if it does, the law of diminishing returns nowhere operates with greater force than in this field. Nowadays when anyone with a modicum of talent can receive free university education in most prosperous countries, the recipients do not appreciate their good fortune nearly as much as we, the older generation did, to whom higher education was still an honor and privilege. I am not advocating the other extreme. Surmounting all obstacles *per ardua ad astra* demands a stronger character than most of us possess. But removing all the *arduum* is a mistake. People do not appreciate something that comes too easily or is indeed thrown at them.

I am convinced that in some cases a surfeit of money is a positive disadvantage. At least, this was the impression I had in my nodding acquaintance with cancer research. A sum of money will always find outlets, if not usefully, then wastefully. Whenever I see six highly qualified authors to a not very



significant paper I cannot help wondering what their individual contributions were. Was the last one the spelling expert? Or for instance are those innumerable congresses really necessary, or just means of draining surplus funds?

In my opinion the most useful change in the present system of allocating funds for research would be to tie a certain part of the grant to achievement. Human nature being as it is, a judicious combination of the stick and the carrot is likely to bring better results than either an oversized stick, or an oversized carrot by itself. Granting agencies wield a miniature stick in that they can demand progress reports and withhold further allocations, but they have no carrot to offer. The grant is received by the grantee whether he makes a half-hearted or a whole-hearted effort and irrespective of the importance of his work. I do of course realize that the object of a research grant is to make research possible, hence it has to be paid out while the research is in progress, but it also has the object of getting the best return for the outlay of large sums of money. This end would be better served if the research workers were given some incentive to do their work quickly and efficiently. At present the end of a research project, at least to some of the participants, may mean the end of a secure, comfortable and undemanding period which they may want to continue as long as possible.

An incentive could be provided by awarding minimal grants while a project is in progress, with the promise of a merit award when it is finished. This award could be made more for meritorious than for indifferent work. One possible way of its administration could be the subsidizing of high ranking journals, enabling them to pay their contributors at equal rates to popular press, and publishers to pay authors whose work is too specialized to command large sales. Another possibility would be to set prizes at a much less exalted level than the one in a million chance prizes like the Nobel prize.

May I also comment on the recommendation of the Editors of channeling more effort into theoretical work than is done at present. By a somewhat superficial analogy, theorizing has often been compared with fitting pieces of a jigsaw puzzle together. This may be apt in some fields of medical research, it certainly does not apply to others. Biochemistry, for instance, seems comparable to a tree with the skeleton clearly visible, and the work of contemporary science is to follow it through to its branches and branchlets. There seems no need for theories, new research is largely a matter of finding new facts. It is in such fields where twentieth century science has done truly magnificent work. I remember reading an anecdote in the *Readers Digest* of a country doctor working in the early decades of this century, to whom asking his patients for a sample of urine was an expedient for getting his tonic bottles back. A good deal of distance seems to stand between his surgery and the Pathologic Laboratory of a modern hospital.

Some pathologic phenomena, like carcinogenesis or atherogenesis, are still unexplored. Experience shows that important prophylactic and therapeutic measures can be put in practice long before the causation of a disease is understood, but in such cases research is of the nature of groping in the dark and progress can be agonizingly slow. It is in the fields where there is a great need for scientists who are capable of fitting the jigsaw pieces together and bringing nearer an understanding of etiologic and pathogenetic factors.

Here I believe the basic difficulty is that the common usage of the word research means only experimentation and data collecting, irrespective of whether in that particular field there is a need for theorizing or not. For instance, when applicants for a research grant are asked for details of their research plan, the description of the experiments they propose to carry out, the animals they will use, etc., they are clearly given to understand that the granting authority uses the term 'research' in this sense and the kind of application they expect to receive will be of the nature of: The effect of dopamine on the intestinal circulation of Vitamin A deficient rats. By not giving even a hint that they are willing to consider theorizing as research, the authorities tend to perpetuate the present state with a disproportionate stress on experimentation and data collecting. In other words, while it is generally recognized that the experimenter and data collector has to eat while doing not immediately useful work, it is apparently not recognized that the theoretician also has to do so. Admittedly the theoretician does sedentary work and his caloric requirements are likely to be less than those of his physically more active fellows, but it may be useful to point out that even he needs an occasional square meal.

Disproportionate stress on data collecting and experimentation is somewhat reminiscent of a police force whose duties consist solely of taking fingerprints and picking up cigarette ends, without anyone correlating information and drawing conclusions.

Stephen Seely BSc  
3 Truro Drive  
Sale, Cheshire M33 5DF  
England

#### REFERENCE

1. Burch G F. Of venture research. *AM HEART J* 92: 681 1976.

#### Potassium and salt substitutes

##### To the Editor

It is uncommon today to see a medical journal without some advertisements for generic names used as potassium supplements. I would like to advocate an inexpensive source of potassium supplement usually unadvertised.

Most of the available salt substitutes contain potassium chloride as the major ingredient. One gram contains 11 to 19 mEq of potassium and a negligible amount of sodium (less than one mEq per 100 grams). Some of these salt substitutes are available in small packages 1/2 or one gram. These small packages are an inexpensive and convenient source of potassium supplement in addition to the original use as a salt substitute.

A few complications have been reported with the commonly used potassium supplements, perhaps the use of a salt substitute as a potassium supplement would have no complication other than hyperkalemia.

Ali Haddad MD  
Director Hemodialysis Unit  
Veterans Administration Hospital  
Iron Mountain, Mich 49801

# REFERENCES

- 1 Pearson R E and Rish K H Potassium content of selected medicines foods and salt substitutes Hosp Pharmacy 9 1971
- 2 19 6 Physicians Desk Reference 30th ed pages 1549 and 1667 Oradell, N J 1976, Medical Economics Company

## Computerized electrocardiography

### To the Editor

In the December 1976 issue of AMERICAN HEART JOURNAL, (97 773 780) Drs Burchell and Reed reported on A test experience with a machine processed electrocardiography diagnosis. The recognition of "normal and some specific patterns". Two serious errors appear in the article which require immediate correction (1) The title of the computer print-out p 778 states Sinai/Bonner ECG Analysis and (2) lines 2 and 3 of the summary on p 780 refer to commercially available IBM Bonner Mt Sinai System.

Initially I did work at Mt Sinai Hospital in New York in conjunction with IBM and Dr Bonner's staff. This effort was terminated in 1968 69. At present among the commercially available programs there is the IBM Bonner program as studied by Drs Burchell and Reed in this article and a distinctly different Mt Sinai Hospital/Cro Med Biomed Corporation system. Since I have personally studied many of the computer ECG programs available I do agree in principle with the findings of Burchell and Reed concerning the IBM Bonner ECG program as reported.

For perspective a good review appeared in the September 1976 issue of The American Journal of Cardiology (38 362 376) by Dr Cesar A. Caceres. A study of a detailed analysis of the performance of the Mt Sinai/Cro Med system in Brussels in over 23 000 cases was published by J. Enderle and associates. In a recently published book I have covered the current status of computerized electrocardiography.

Leon Fordy M.D. F.A.C.C.  
Clinical Associate Professor  
of Cardiology & Associate  
Cardiologist at the Mount  
Sinai Medical Center  
Fifth Avenue & 100th St  
New York N.Y. 10029

# REFERENCES

- 1 Burchell H B and Reed J. A test experience with a machine processed electrocardiography diagnosis. The recognition of normal and some specific patterns. AM HEART J 92 773 1976
- 2 Caceres C A. Limitations of the computer in electrocardiographic interpretation. Am J Cardiol. 38 367 1976
- 3 Enderle J, Telesman M, Fordy L, Chesky H and Jaffe H. Computer interpretation of electrocardiograms and vectorcardiograms, in Advances in Cardiology 16 194 1976 Basel 1976 S. Karger AG
- 4 Fordy L. Computer electrocardiography: Present status and criteria. Mount Kisco N.Y. Dec 1977 Futura Publishing Co.

# Book reviews

**Pre Excitation** By M Irene Ferrer Mount Kisko New York 1976 Futura Publishing Company Price \$27.50

Much has been written over the past few decades about the pre excitation state. This reviewer wonders if so much concern over this one electrophysiologic state is justified. It is intriguing and interesting and of great importance to the patient who has the syndrome and to the physician in charge who must contend with its many facets and complications. But so much has been written on this subject that it would be almost impossible for someone to be thoroughly acquainted with the entire literature on this subject. This is even evident in this monograph.

The book describes the mechanisms associated with arrhythmias significance and management very well. The illustrations are well selected and the legends are very good. Readers should remember that the functional state and the influence of the time course of the order of activation of more than one wave front on the completed electrocardiogram are important as well as underlying myocardial disease. The role and even existence of special tracts near the A-V node needs careful consideration. It is because of these important associated factors that so much interest in the pre excitation syndrome has been created. This is a very good book on an interesting electrophysiologic and clinical state in cardiology.

✓ **Physiological and Clinical Aspects of Cardiac Auscultation** By Dr Alan Harris Dr George Sutton and Dr Malcolm Towers Philadelphia 1976 J B Lippincott Company 416 pages Price \$48.00

This is an excellent book for all doctors especially medical students housestaff and all trainees in medicine. The use of auscultation in medicine is a dying art even though it is most important for good clinical cardiology. The contributors are excellent clinicians who have developed their respective contributions well. The book correlates the findings by auscultation with the hemodynamic clinical pathologic and echo cardiographic and other recordings very well. The use of many illustrations excellent ones in color along with a brief well written text is most effective. This is a highly recommended book.

✓ **Neural Regulation of the Heart** Edited by Walter C Randall Ph.D New York 1977 Oxford University Press Price \$21.95

This book emphasizes the role of the nervous system in cardiac regulation in the normal heart and its influence on abnormal cardiac states. Interest in the influence of the nervous system on cardiac function commanded the attention of physiologists during the first part of this century. In more

recent years this interest was replaced by studies of hemodynamic phenomena. This change is interesting since it reflects the tendency to emphasize one aspect of cardiovascular physiology to the exclusion of another. Any clinician and investigator knows that no aspect of cardiovascular physiology can be ignored. All aspects are important and enjoy an integrated role among all others. This book edited by Randall summarizes selected aspects of the role of the nervous system in cardiac function. The various contributors review studies and thoughts lucidly. Because each contributor presents his isolated portion to the book the book fails to represent the characteristics of a monograph written by one author but represents more a series of papers which are somewhat disconnected from the others. Regardless this is an extremely important subject in need of greater attention and study. Randall's book should stimulate clinical and laboratory research in the subject of the nervous control of the heart and circulation. Therefore this is a good and welcome publication which contains a great deal of useful information. Critical study of the book can be rewarding to all physicians and physiologists interested in the heart and circulation. The book is a good one worth owning for repeated study. The anatomic and physiologic presentations are good and important.

✓ **Cardiovascular Physiology Third Edition** By Robert M Berne and Matthew N Levy Saint Louis 1977 The C V Mosby Company 282 pages Price \$9.95

This is a brief and nicely written and well illustrated review of cardiovascular physiology. The authors are physiologists with experience and interest in cardiovascular physiology who have been teaching the subject for many years. The selected aspects of cardiovascular physiology described are important ones for learning cardiovascular physiology. This book should interest clinicians as well as physiologists since the principles discussed are fundamental ones. The material referred to in the bibliographies are mainly rather recent. The classic publications of Frank Wilson Craib Wolferth and others are not even listed. Lewis and Wilson have contributed extensively to electrocardiography and electrophysiology. Yet their publications and those of others are not listed. The same is true of the early and fundamental basic studies related to the cardiac pump. Regardless this is an excellent review for students housestaff and physicians and serious investigators will find this to be a good start on important subjects of cardiovascular physiology. It is obvious that the authors have designed the book for medical and graduate students as they indicate in their preface. This teaching objective is well achieved. It is highly recommended for them but it hoped that the next edition or printing will include references to the classics in cardiovascular physiology which should stimulate students to enter full time careers in physiology and academic medicine.

## Books received

---

**Current Concepts in Radiology vol three** Edited by E. James Potchen M.D. St. Louis 1977 The C V Mosby Company 42 pages Price \$39.50

**The Biochemistry of Smooth Muscles** Edited by Newman I. Stephens, M.D. Baltimore 1977 University Park Press 718 pages Price \$34.50

**A Diagnostic Approach to Chest Diseases 2nd edition Differential Diagnoses Based on Roentgenographic Patterns** By Glen A. Lillington and Robert W. Jamphs Baltimore 1977 The Williams & Wilkins Company 591 pages Price \$54.00

**Beta adrenergic Blockers and Hypertension** Edited by D. Ganten R. Dietz B. Luth and F. Gross, Stuttgart Germany 1976 Georg Thieme Verlag 201 pages

**Recent Advances in Blood Coagulation** Edited by Leon Poller New York 1977 Churchill Livingstone 377 pages. Price \$35.00

**Low Density Lipoproteins** Edited by Charles E. Day and Robert S. Levy New York 1977 Plenum Publishing Corporation 433 pages Price \$39.50

# Announcements

## Refresher course in cardiac imaging

A refresher course in cardiac imaging will be presented by the North American Society for Cardiac Radiology March 20 through 24 1978 at the MGM Grand Hotel Las Vegas Nevada

The program will follow the standard format of morning lecture series followed by afternoon workshops Faculty members of internationally known authorities in cardiology radiology ultrasound nuclear medicine and computerized tomography will direct the program The course is sponsored by the American College of Radiology and the council on Clinical Cardiology of the American Heart Association and will offer approximately 23 hours of credit for Category I of the AMA Physician's Recognition Award

For further program content information please contact Dr Richard H Jaffe telephone (801) 328 9061 ext 225 or write Teri Dibble Conferences and Institutes Division of Continuing Education University of Utah 1152 Annex Building Salt Lake City Utah 84112

## Workshop in Echocardiography

A Workshop in Echocardiography will be held at the Newporter Inn Newport Beach California on January 25 through 28 1978 The workshop will be directed by Louis Evan Teichholz MD Associate Chief of Cardiology Mount Sinai Medical Center and Associate Professor of Medicine Mount Sinai School of Medicine New York For further information regarding this workshop please contact Ms Billie N Chiles Tampa Trainings P O Box 1245 Tarpon Springs Fla 33589

## Fifth International Congress on Electrocardiology

The Fifth International Congress on Electrocardiology will be held in Glasgow Scotland on September 5 through 8 1978 There will be sessions on Programmed Electrocardiography (Pacing Studies) Cardiac Electrophysiology Mathematical Modelling Dynamic Electrocardiography ECG Criteria Exercise Electrocardiography and Computer Studies in Electrocardiography Full details of the Congress can be obtained from the Congress Secretariat University Department of Medical Cardiology Royal Infirmary Glasgow G4 0SF Scotland

## Optical microscopy and photomicrography in the biomedical sciences

The Marine Biological Laboratory Woods Hole Massachusetts announces Optical Microscopy and Photomicrography

in the biomedical sciences a residential laboratory course March 12-18 1978 This concentrated program is intended primarily for scientists and physicians who require theoretically based training and experience in modern light microscopy Among the topics to be discussed and practiced will be bright and dark field phase and modulation contrast high extinction polarized light and differential interference microscopy fluorescence and color and black and white photomicrography and cinemicrography The Instructor in Chief will be Robert Day Allen of Dartmouth College Additional information and application materials may be obtained from the Director of Admissions Marine Biological Laboratory Woods Hole Mass 02543 phone 617 548 3705

## Intra aortic balloon pump symposium

Daniel Freeman Memorial Hospital Inglewood (Los Angeles) California presents A Symposium on Clinical and Technical Application of the Intra Aortic Balloon Pump on March 10-11 1978 at the Pacific Hotel in Culver City California

Up to fifteen hours of Formal (Category 1) credit towards the California Medical Association Certificate in Continuing Medical Education and the American Medical Association Physicians Recognition Award may be reported State of California Provider No 00075R N allows ten contact hours of Continuing Nursing Education Fee for physicians \$100.00 Fee for RN \$75.00

For further information please contact Valene Grace RN Department of Education Daniel Freeman Memorial Hospital 333 North Prairie Avenue Inglewood California 90301 Telephone (213) 674 7050 extension 111

## Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal, and has not been previously published Authors will be consulted when possible regarding republication of their material

## Editorial

### Can death from venous thromboembolism be prevented in elderly patients with hip fractures?

G Keith Morris MD  
J R A Mitchell MD  
Nottingham England

To enable elderly patients with hip fractures to walk again as soon as possible after their injury stabilization of the fracture by a pinning operation or replacement of the femoral head is commonly undertaken. Among the benefits claimed for early operation and walking is the avoidance of those complications which are attributed to prolonged bed rest—muscle wasting, osteoporosis, hypostatic pneumonia and bedsores. While early mobilization could theoretically help to reduce the frequency of venous thromboembolism in practice pulmonary embolism remains a serious problem and kills approximately one out of every ten patients within three months of their injury. Pulmonary embolism however can be prevented in these very high risk patients. This was demonstrated convincingly in 1959 by the clinicopathological study of Savitt and Gallagher in which treatment with an oral anticoagulant markedly reduced the frequency of venous thrombosis and eliminated the risk of fatal pulmonary embolism. The efficacy of prophylactic anticoagulation in preventing pulmonary embolism has been reaffirmed on many occasions but it has become clear that the reduction in overall mortality which can be achieved by oral anticoagulation is not as great as was originally

suggested because diseases other than venous thromboembolism kill many of these elderly and infirm patients.<sup>1</sup>

Despite its proven efficacy in preventing death from pulmonary embolism prophylactic anticoagulation is unpopular. In 1973 a survey of antithrombotic practices in orthopedic surgery in the USA suggested that only 11 per cent of surgeons used prophylactic anticoagulation routinely in the management of elderly patients with hip fractures while a further 36 per cent offered treatment to selected patients. More recently in a similar survey in the United Kingdom we found that only 3 per cent of orthopedic surgeons routinely used prophylactic anticoagulation in patients with hip fractures. If they are not using anticoagulants have orthopedic surgeons discovered a more convenient and equally effective alternative form of prophylaxis?

As judged by the surveys<sup>2,3</sup> about one third of orthopedic surgeons in the USA and about a half of their British colleagues offer no prophylactic treatment whatsoever and small groups of surgeons in both countries use dextran, aspirin, combinations of dextran and aspirin and low dose heparin on a prophylactic basis. Those who use dextran can quote studies which support the value of this agent but scrutiny of the literature concerning prophylaxis with dextran in hip fracture patients and in general surgical patients reveals an amazing lack of consistency. Evidence can be marshalled to support four view points—that dextran prevents venous thrombo-

From the University Department of Medicine, Nottingham England.

Received for publication May 23, 1977.

Reprint requests: G Keith Morris MD DSc of Medicine University of Nottingham, The General Hospital, Nottingham NG1 6HA, England.

sis<sup>6</sup> that it does not prevent venous thrombosis,<sup>7</sup> that it prevents pulmonary embolism,<sup>8</sup> and that it does not prevent pulmonary embolism.<sup>9</sup> Trials of poor design variations in the dose and types of dextran used and differing trial endpoints have undoubtedly led to confusion about this agent and there is clearly a need to evaluate it once and for all in an adequately controlled trial using mortality from pulmonary embolism as a firm endpoint. Aspirin too, has proved disappointing in preventing venous thrombosis in groups of patients at lesser risk than those with hip fractures.<sup>10</sup> Zekert and colleagues,<sup>11</sup> however, claimed that prophylactic treatment with aspirin prevented both venous thrombosis and fatal pulmonary embolism in these patients, but their results lack confirmation. In our own studies of venous thromboembolism in elderly patients with hip fractures we found no evidence to indicate that agents which modify platelet behavior (dipyridamole, dipyridamole plus aspirin, and flurbiprofen) could influence the frequency of isotopically diagnosed venous thrombosis. We also failed to confirm that low dose heparin can prevent venous thrombosis in patients with hip fractures.<sup>12</sup> It seems to us unlikely that lengthy studies of these agents using mortality as an endpoint, can be justified.

Thus at present oral anticoagulation is the only regime which has been proved to prevent venous thrombosis and pulmonary embolism in elderly patients with hip fractures. To those surgeons who offer prophylactic anticoagulation to previously fit patients with hip fractures whose premature death from pulmonary embolism would be untimely we would say that they are acting in accordance with the evidence available, to those who offer alternative forms of prophylaxis we would urge them to critically appraise the conflicting evidence so far available while to those who offer no prophylaxis at all we would

remind them that they are allowing a number of pulmonary embolic deaths to occur in patients who could otherwise have survived to live an independent and useful life.

#### REFERENCES

1. Sevitt S and Gallagher N G. Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle aged and elderly patients with fractured necks of femur. *Lancet* 2 981 1959.
2. Morris G K and Mitchell J R A. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. *Lancet* 2 869 1976.
3. Salzman E W, Harris W H and de Sanctis R W. Anticoagulation for prevention of thromboembolism following fractures of the hip. *N Engl J Med* 275 122, 1966.
4. Simon T L and Stengle J M. Antithrombotic practice in orthopaedic surgery. *Clin Orthop* 102 181 1974.
5. Morris G K and Mitchell J R A. Prevention and diagnosis of venous thrombosis in patients with hip fractures. *Lancet* 2 867 1976.
6. Ahlberg A, Nylander G, Robertson B, Cronberg S and Nilsson I M. Dextran in prophylaxis of thrombosis in fractures of the hip. *Acta Chir Scand (Suppl)* 387 63 1968.
7. Daniel W J, Moore A R and Flanc C. Prophylaxis of deep vein thrombosis with dextran 70 in patients with fractured necks of femur. *Aust N Z J Surg* 41 289 1972.
8. Kline A, Hughes L E, Campbell H, Williams A, Zlosnick J and Leach K G. Dextran 70 in prophylaxis of thromboembolic disease after surgery. A clinically orientated randomised double blind trial. *Br Med J* 2 109 1975.
9. Brisman R, Parks L C and Haller J A. Dextran prophylaxis in surgery. *Ann Surg* 174 137 1971.
10. Report of the steering committee of a trial sponsored by the Medical Research Council. Effect of aspirin on postoperative venous thrombosis. *Lancet* 2 441 1972.
11. Zekert F, Kohn P and Vormittag E. Prophylaxis of thromboembolic diseases in traumatologic patients. A randomised double blind study with acetylsalicylic acid. In Proceedings of Fourth Congress of the International Society of Thrombosis and Haemostasis Vienna 1973 p 245.
12. Morris G K and Mitchell J R A. Preventing venous thromboembolism in elderly patients with hip fractures. Studies of low dose heparin, dipyridamole, aspirin and flurbiprofen. *Br Med J* 1 535 1977.

## Intrapulmonary acetylcholine in bilharzial cor pulmonale

M M Abdel Fattah MD

A Abou Zeina MD

A M Nomer MD

H Badawi MD

M Salah FRCP

Alexandria Egypt

Intrapulmonary infusion of acetylcholine dilates the small pulmonary arterioles and decreases the pulmonary arterial pressure as it traverses the lung it is completely inactivated and so it has no effect on the systemic blood pressure or heart rate. Bishop and associates<sup>1</sup> found that infusion of acetylcholine in the pulmonary artery of patients with mitral stenosis produced a small fall in the mean pulmonary artery pressure and a negligible fall in the mean arterial oxygen tension without any change in the alveolar oxygen tension.

In a healthy subject breathing room air the small difference between the alveolar and arterial oxygen tensions (A-a difference) is due to the normally occurring small right to left shunting and uneven distribution of the pulmonary blood flow relative to alveolar ventilation. The A-a difference also depends on the diffusing capacity of the alveolar capillary membrane. The diffusion component is extremely small in normal subjects breathing room air and is nullified by breathing oxygen enriched mixtures. Such high oxygen mixtures also correct the ventilation component of the ventilation-perfusion imbalance. Thus at high levels of alveolar oxygen any A-a oxygen difference is almost entirely due to anatomical right to left shunts.

Bilharzial cor pulmonale is a chronic vascular cor pulmonale due to widespread affection of the small pulmonary arteries. Zaki and col-

leagues<sup>2</sup> were of the opinion that in this disease besides the systolic overloading of the right ventricle there is also a diastolic overload. The latter is due to various vascular shunts namely intrasplenic, porto-pulmonary, bronchopulmonary and pulmonary arteriovenous. Although these shunts were demonstrated yet they were not quantitated. Some of these shunts can explain arterial hypoxemia met with in some patients with bilharzial cor pulmonale.

The aim of this work is a further study of the mechanisms of pulmonary hypertension in bilharzial cor pulmonale and the arterial hypoxemia found in some patients with this disease.

### Material and methods

Fifteen male bilharzial patients with clinical, radiological and electrocardiographic evidence of cor pulmonale were studied. Their ages ranged between 11 and 47 years. All had bilharzial hepatic fibrosis and splenomegaly. None had any episode of gastro-oesophageal bleeding. Five had ascites (Nos 2, 4, 8, 11 and 12). All had a hemoglobin level above 7.0 per cent and were free of respiratory diseases.

Conventional right heart catheterization was performed and pressures at different sites of the right side of the heart and the pulmonary circuit were obtained. All pressures were measured with the zero point 5 cm below the sternal angle in the supine position. The cardiac output was calculated according to the Fick principle and the pulmonary vascular resistance was derived. In three patients in whom the pulmonary artery pressure was normal at rest (Nos 2, 7 and 8) an exercise test was performed to prove the presence of early cor pulmonale.

Ten mg of acetylcholine diluted in 10 ml saline

From the Cardiac and Respiratory Unit, Faculty of Medicine, Alexandria, Egypt.

Received for publication August 18, 1976.

Accepted for publication December 17, 1976.

Reprint requests: A. Abou Zeina, MD, Cardiac and Respiratory Research Centre, Faculty of Medicine, Alexandria University, Alexandria, Egypt.



Table I Hemodynamics in bilharzial cor pulmonale

| Patient no | Age | Mean P.A.P* (mm Hg) |                |          | PCP | Resting CO (Litres/min) | Resting PVR (units) |
|------------|-----|---------------------|----------------|----------|-----|-------------------------|---------------------|
|            |     | Rest ing            | After exercise | After AC |     |                         |                     |
| 1          | 16  | 77                  |                | 60       | 5   | 7.00                    | 8.30                |
| 2          | 47  | 12                  | 21             |          | 8   | 12.55†                  | 9.45                |
| 3          | 36  | 48                  |                | 45       | 9   | 4.80                    | 11.30               |
| 4          | 35  | 34                  |                | 27       | 7   | 10.30†                  | 2.80                |
| 5          | 32  | 63                  |                | 63       | 8   | 5.28                    | 11.70               |
| 6          | 40  | 43                  |                | 44       | 10  | 5.40                    | 6.40                |
| 7          | 15  | 11                  | 19             | —        | 10  | 6.80                    | 1.50                |
| 8          | 40  | 7                   | 20             |          | 9   | 11.40†                  | 0.56                |
| 11         | 28  | 61                  |                | 61       | 8   | 5.90                    | 8.30                |
| 10         | 35  | 73                  |                | 73       | 8   | 5.78                    | 10.60               |
| 11         | 15  | 54                  |                | 54       | 6   | 4.70                    | 11.06               |
| 12         | 11  | 35                  |                | 35       | 10  | 8.20                    | 3.70                |
| 13         | 20  | 36                  |                | 35       | 8   | 6.90                    | 5.70                |
| 14         | 24  | 53                  |                | 52       | 9   | 6.71                    | 7.00                |
| 15         | 25  | 40                  |                | 26       | 8   | 8.00                    | 8.20                |

Abbreviations P.A.P. = Pulmonary artery pressure CO = Cardiac output PVR = Pulmonary vascular resistance AC = Acetylcholine PCP = Precapillary wedge pressure

†The high cardiac output in patients Nos 2, 4 and 8 can be due to the hyperkinetic circulation and hypervolemia frequently met with in patients with advanced bilharzial liver fibrosis and ascites

were infused into the pulmonary artery via the cardiac catheter over a period of ten minutes, i.e. at a rate of one mg./minute. In patients Nos 3, 9 and 15 only 5 mg. of acetylcholine were infused at the same rate i.e., during five minutes. Arterial blood samples were taken via an indwelling arterial needle before, at the middle and at the end of the infusion i.e., after the infusion of 5 or 10 mg. of acetylcholine. Arterial samples were taken repeatedly after the end of the infusion for a period of six to ten minutes. The per cent oxygen saturation of the blood samples was determined by oximetry. The pulmonary artery pressure was determined before and at the end of infusion. The heart rate and the systemic arterial blood pressure were also followed all through the experiment and the chest was auscultated for evidence of bronchospasm during and after acetylcholine infusion. In all patients receiving 10 mg. acetylcholine except patient No 1 the whole procedure was repeated while the patients were breathing 100 per cent oxygen. The oxygen inhalation was maintained via an oxygen mask for five minutes before and all through the acetylcholine experiment.

The acetylcholine experiment was also per-

formed on four healthy normal control subjects but to avoid catheterization of healthy subjects 10 mg. of the drug were infused via the antecubital vein.

## Results

The pertinent hemodynamic data are listed in Table I. The pulmonary artery pressure was elevated in all the patients except Nos 2, 7, and 8 in whom it was normal at rest but showed an abnormal increase after exercise, and who were considered as early cor pulmonale patients. These three patients were included in the study before catheterization because of positive clinical, radiological, and electrocardiographic signs of cor pulmonale. The per cent oxygen saturation of the arterial blood at rest while breathing room air ranged between 94.5 and 99 in all the patients except patient No 4, who had 89.5 per cent saturation (Table II). After breathing 100 per cent oxygen the arterial oxygen saturation ranged between 97 per cent and 100 per cent in all the patients including patient No 4 who had arterial desaturation while breathing room air (Table III).

**Acetylcholine experiment** The effects of acetylcholine on arterial oxygen saturation while the patients were breathing room air are shown in Table II. Fig. 1 shows the average effects of the infusion of 10 mg. acetylcholine in three patients with early cor pulmonale, in 12 patients with moderate to severe cor pulmonale, and in four normal subjects. The figure also shows the average results of the infusion of only 5 mg. acetylcholine in three patients. In all the patients there was an evident drop in arterial oxygen saturation after the infusion of 5 mg. acetylcholine and the drop was more evident as the infusion continued to 10 mg. The drop persisted for about two minutes after the end of the infusion and gradually improved during the following eight minutes but did not reach the pre-infusion level. In eleven of the patients who had intrapulmonary injection of 10 mg. acetylcholine the experiment was repeated while they were breathing 100 per cent oxygen (Table III). In five patients there was no change in arterial oxygen saturation; in four patients there was a drop of 1 per cent; and in the remaining two patients (Nos 7 & 14) the saturation dropped from 98.5 and 97 per cent respectively, before infusion to 94 per cent for both of them after infusion.

Table II Arterial oxygen saturation while breathing room air at rest before and at the end of 5 and 10 mg Acetylcholine infusion and every two minutes thereafter

| No              | Before<br>A.C. | 5<br>mg<br>A.C. | 10<br>mg<br>A.C. | 2<br>min<br>after | 4<br>min<br>after | 6<br>min<br>after | 8<br>min<br>after | 10<br>min<br>after |
|-----------------|----------------|-----------------|------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| <b>Patients</b> |                |                 |                  |                   |                   |                   |                   |                    |
| 1               | 97.0           | 95.5            | 94.0             | 93.0              | 95.0              | 96.5              | 95.0              |                    |
| 2               | 96.5           | 87.0            | 80.5             | 84.5              | 86.5              | 87.0              | 87.0              |                    |
| 3               | 95.5           | 97.0            |                  | 97.0              | 87.5              |                   | 88.0              |                    |
| 4               | 89.5           | 88.0            | 86.5             | 87.0              | 86.5              | 86.5              | 86.5              | 88.0               |
| 5               | 94.5           | 90.0            | 88.0             | 87.0              |                   |                   |                   | 91.0               |
| 6               | 93.0           | 69.5            | 87.0             | 88.5              |                   | 89.5              | 93.0              | 95.0               |
| 7               | 96.5           | 9.5             | 90.5             | 91.0              | 90.5              | 90.0              | 69.5              | 88.0               |
| 8               | 94.5           | 89.0            | 84.0             | 8.0               | 89.0              | 90.0              | 90.0              | 97.0               |
| 9               | 95.0           | 93.0            |                  | 91.5              | 91.5              |                   |                   |                    |
| 10              | 94.5           | 90.0            | 96.5             | 94.0              |                   | 94.0              |                   |                    |
| 11              | 85.0           | 88.0            | 84.0             | 86.0              |                   |                   |                   |                    |
| 12              | 97.0           | 94.0            | 96.0             |                   |                   | 99.5              |                   |                    |
| 13              | 95.0           | 97.0            | 93.5             | 94.5              |                   | 94.5              |                   |                    |
| 14              | 96.0           | 89.5            | 86.5             |                   |                   |                   |                   | 91.0               |
| 15              | 90.5           | 91.0            |                  | 97.5              | 92.0              |                   |                   |                    |
| <b>Normals</b>  |                |                 |                  |                   |                   |                   |                   |                    |
| 1               | 95.0           | 93.0            | 95.0             |                   | 94.0              |                   |                   |                    |
| 2               | 95.0           | 9.0             | 99.5             |                   | 94.0              |                   |                   |                    |
| 3               | 98.0           | 90.5            | 96.5             |                   | 88.5              |                   |                   |                    |
| 4               | 99.5           | 98.0            | 94.0             |                   |                   |                   |                   |                    |

A.C. = Acetylcholine

In the normal subjects breathing room air the arterial oxygen saturation showed a mild reduction during and after acetylcholine infusion via the antecubital vein the average reduction was 3 per cent only (Fig. 1) While breathing 100 per cent oxygen acetylcholine did not change the arterial oxygen saturation in any of the normal subjects

### Discussion

Bilharzial cor pulmonale is primarily due to widespread affection of small pulmonary arteries by obliterative changes. Many workers from Alexandria explained the pathologic physiology of this disease. Badawi and co workers<sup>1</sup> are of the opinion that the whole picture in bilharzial cor pulmonale can be explained by fixed widespread obliterative arteritis affecting the small pulmonary arteries. Zaki and co workers<sup>2</sup> on the other hand believe that besides this important factor various shunts at different levels as well as hypervolemia contribute to the hemodynamics of the disease. They stressed the role of protozoan and porto pulmonary venous shunts as well as

Table III Arterial oxygen saturation while breathing room air and 100 per cent oxygen before and after acetylcholine

| Patient<br>no | Oxygen<br>per cent<br>at room<br>air | Oxygen per cent during<br>oxygen inhalation |                        |
|---------------|--------------------------------------|---|------------------------|
|               |                                      | Before<br>acetylcholine                     | After<br>acetylcholine |
| 2             | 95.5                                 | 99.5  | 98.0                   |
| 4             | 89.5                                 | 90.5  | 98.5                   |
| 5             | 94.5                                 | 100.0                                       | 100.0                  |
| 6             | 95.0                                 | 98.5  | 98.5                   |
| 7             | 86.5                                 | 98.5  | 94.0                   |
| 8             | 94.5                                 | 99.5  | 99.5                   |
| 10            | 94.5                                 | 100.0                                       | 100.0                  |
| 11            | 95.0                                 | 99.0  | 99.0                   |
| 12            | 97.0                                 | 99.0  | 94.0                   |
| 13            | 95.0                                 | 98.5  | 97.5                   |
| 14            | 96.0                                 | 97.0  | 94.0                   |

bronchopulmonary shunts in the pathogenesis of the disease. Porto pulmonary venous shunts and pulmonary arteriovenous shunts were blamed by these authors for the arterial oxygen desaturation which they encountered in some patients with bilharzial cor pulmonale

In the present work the arterial oxygen saturation at rest ranged between 94.5 per cent and 97 per cent except in patient No. 4 in whom it was 89.5 per cent. His resting mean pulmonary artery pressure was 34 mm Hg and he had marked ascites. The ventilatory disturbances associated with marked ascites can contribute to his arterial undersaturation. In fact his arterial oxygen saturation was completely corrected after oxygen inhalation (Table III). It is also interesting to note that acetylcholine infusion in this patient produced a mild but appreciable lowering of his pulmonary artery pressure indicating that a vasoactive component probably due to hypoxia was contributing to his pulmonary hypertension.

Acetylcholine has a dilating effect on the pulmonary arteries and capillaries. The results of this dilating effect are not normally very obvious. The action of any dilating drug will become more obvious if the vessel to which it is applied has previously been constricted. These results are more obvious in pathological pulmonary hypertension in the presence of active vasoconstriction. In bilharzial cor pulmonale the pulmonary hypertension is essentially due to organic obliterative

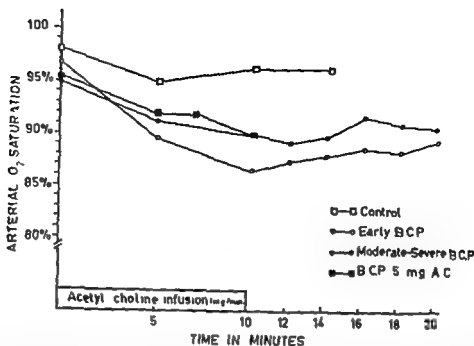


Fig 1 Average changes in arterial oxygen saturation after intravenous infusion of 10 mg acetylcholine in four normal subjects (control) and the intrapulmonary infusion of 5 mg (three patients) or 10 mg (12 patients) with bilharzial cor pulmonale (BCP) (three patients with early and nine with moderate to severe BCP)

ative arteritis and our previous experience with acetylcholine<sup>3</sup> failed to show any effect of this drug even on the post exercise elevation of the pulmonary artery pressure. In the present study we could also not detect any effect of acetylcholine infusion on the levels of the pulmonary artery pressures except in three patients Nos 1, 4 and 15. In these patients there was a mild reduction in the pulmonary artery pressure after acetylcholine infusion which denotes the presence of a vasospastic element. Hypoxia can be a factor only in patient No 4, an active stage of arteritis can explain the spasm in all the three patients. De Faria and associates<sup>4</sup> demonstrated a vasospastic factor in their patients with bilharzial cor pulmonale.

In all patients studied, there was a reduction in the arterial oxygen saturation by intrapulmonary acetylcholine infusion. This reduction without lowering of the pulmonary artery pressure indicated that the action of acetylcholine in bilharzial cor pulmonale was distal to the small pulmonary arteries, i.e., in the territories of rich precapillary and capillary anastomosis in the vicinity of the alveoli and distal air passages. Tarabeh<sup>10</sup> found reduced compliance and increased work of breathing in bilharzial cor pulmonale while Abdel Rassoul<sup>11</sup> demonstrated in his series uneven ventilation. These ventilatory disturbances and the obliterative changes in the pulmo-

nary arteries are mainly focal and disturb the ventilation/perfusion ratio. This defect will become more manifest if it is further disturbed by dilatation of the vessels supplying hypoventilated alveoli. Furthermore, intrapulmonary injection of acetylcholine can lead to narrowing of the distal respiratory passages with hypoventilation of their corresponding alveoli thus accentuating the disturbed ventilation/perfusion ratio. However, auscultation of the patients during and after acetylcholine infusion failed to reveal evidence of bronchospasm, but this does not rule out spasm of distal bronchial passages. The fact that arterial oxygen undersaturation after acetylcholine was completely corrected by 100 per cent oxygen inhalation indicates that hypoventilation was the main factor in the production of arterial hypoxemia. It is thus logical to assume that the mechanism of arterial oxygen undersaturation after acetylcholine in our patients was related to selective opening up of vessels supplying underventilated segments of the lungs. The same explanation has been suggested for similar results in pulmonary hypertension due to mitral stenosis<sup>2, 12</sup> (Soderholm and Werko 1959; Harris 1961 and Bishop et al 1962).

We can deduce that the arterial oxygen desaturation which occurs in some patients with bilharzial cor pulmonale results from a disturbed ventilation/perfusion ratio. The fact that oxygen

inhalation corrected the arterial desaturation in patient No 4 and prevented the occurrence of arterial desaturation in all the patients except two after acetylcholine infusion confirms this suggestion. Porto pulmonary shunts were considered important in the production of arterial oxygen desaturation in bilharzial cor pulmonale. The oxygen saturation of portal blood is relatively high and averages 78 per cent and therefore porto pulmonary shunts cannot produce appreciable arterial desaturation unless the venous admixture is great; furthermore it should not be completely corrected by oxygen inhalation. Patients Nos 7 and 14 had arterial oxygen saturation of 96.5 and 96 per cent respectively at rest. Acetylcholine infusion while breathing room air diminished the saturation to 88 and 86.5 per cent respectively. Acetylcholine infusion while breathing 100 per cent oxygen decreased their arterial oxygen saturation only to 94 per cent. Thus 100 per cent oxygen appreciably corrected the desaturation after acetylcholine. The correction can be explained by improving the ventilation/perfusion ratio. These patients apparently had also veno-arterial shunts which were encouraged by acetylcholine and their effect could not be nullified by oxygen inhalation; the shunts however were modest and lowered the arterial oxygen saturation only to 94 per cent.

Fig 1 shows that the effect of acetylcholine infusion in normal subjects were not marked as in bilharzial cor pulmonale. All the figures for the per cent oxygen saturation after acetylcholine in the normal subjects were still within or just below the normal range (Table II). In these subjects acetylcholine was infused slowly via the antecubital vein and it is expected that during its passage from the arm to the lungs part of the drug was deactivated by the choline esterase normally present in the blood.

### Conclusion

The pulmonary hypertension in bilharzial cor pulmonale is mostly obliterative and fixed. Intra-

pulmonary acetylcholine does not decrease the pulmonary hypertension except when a factor of vasospasm is present. Arterial oxygen desaturation is not a feature of bilharzial cor pulmonale and when present it is mild. This oxygen desaturation is predominantly the result of disturbed ventilation/perfusion ratio. Anatomical veno-arterial shunts play only a minor role.

### REFERENCES

- 1 Harris P. Influence of acetylcholine on the pulmonary arterial pressure. *Br Heart J* 19 219 1955.
- 2 Fritts H W, Harris P, Clausen H H, Odell J E and Courmand A. The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. *J Clin Invest* 37 99 1958.
- 3 Bishop J M, Harris P, Bateman M and Raine J M. Respiratory gas exchange in mitral stenosis at three levels of inspired oxygen before and after infusion of acetylcholine. *Clin Sci* 22 53 1962.
- 4 Salah M. Chronic vascular cor pulmonale. Alexandria Med J 4 307 1968.
- 5 Badawi H, Effat H, Khalil H, Nomer A M, and Salah M. Mechanism of pulmonary hypertension in bilharzial cor pulmonale. Alexandria Med J 6 573 1961.
- 6 Zaki H A, El Neneidy A R and Foda M T. Haemodynamic shunts in schistosomiasis cor pulmonale. *Br Med J* 1 367 1962.
- 7 Zaki H A, El Neneidy A R and Khalil M. Use of Krypton<sup>41</sup> in the study of hypoxia in porto pulmonary bilharzias. *Br Med J* 1 1071 1964.
- 8 Harris P. The effects of varying oxygen tension and of acetylcholine in the human pulmonary circulation. London 1961. Ciba Foundation Study Group No 8 J & A. Churchill Ltd.
- 9 De Faria J L et al. Cyanosis in Manson's schistosomiasis. Role of pulmonary schistosomiasis arteriovenous fistulas. *Am Heart J* 54 196 1957.
- 10 Tarabekh A A. Mechanics of breathing in cardiopulmonary bilharzias. Alexandria 1965. M D Thesis. University of Alexandria.
- 11 Abdel Rassoul M Y. Physical efficiency in bilharzial patients. Alexandria 1971. M D Thesis. University of Alexandria.
- 12 Soderholm B and Werko L. Acetylcholine and the pulmonary circulation in mitral valvular disease. *Br Heart J* 21 1 1959.
- 13 Bishop J M, Harris P, Bateman M and Davidson L A G. The effect of acetylcholine upon respiratory gas exchange in mitral stenosis. *J Clin Invest* 40 105 1961.

# Cardiac reserve during isoproterenol stress in patients with aortic valve disease before and after corrective surgery

Franz Schwarz, M D  
Willem Flameng, M D  
Jochen Thormann M D  
Roland Ensslen, M D  
Michael Sesto M D  
Martin Schlepper M D

Bad Nauheim and Giessen West Germany

In a recent report Bailey and associates<sup>1</sup> emphasized that survival after aortic valve replacement in patients with aortic regurgitation depends upon the extent of left ventricular hypertrophy. Bolooki and Kaiser showed that preoperative cardiac function is one of the important determinants of early postoperative survival in patients with aortic valve disease and severe hypertrophy. However, a close relation between left ventricular hypertrophy and function has not been defined previously.<sup>2-4</sup> Further, it is questionable to which extent different types of overload can influence myocardial contractility.<sup>5</sup> Since hypertrophy compensates an increased cardiac stress, we believe that the investigation of cardiac reserve is best suited to study the relation between cardiac hypertrophy and ventricular function. Studies investigating reserve force of the hypertrophied heart muscle are scarce. Indeed, Bolen and colleagues<sup>6</sup> found a deterioration of cardiac function during afterload stress in seven patients with severe aortic regurgitation, two of which however had associated coronary artery disease. Lee and co-workers<sup>7</sup> reported a reduced function during exercise in severe aortic stenosis but not in moderate stenosis. A relation between left ventricular muscle mass and reserve force was not established in these studies.

The purpose of the present study was to quantitatively left ventricular function at rest and during isoproterenol infusion in patients with aortic valve disease and to correlate the reserve force of the left ventricle with the degree of left ventricular hypertrophy.

## Methods

**1 Patients** Preoperative studies were performed in 35 patients undergoing right and left heart catheterization for diagnosis and evaluation of valvular heart disease. There were ten females and 25 males. Each patient gave informed consent for the conduction of the study. No patients received premedication before catheterization. The patients with aortic valve lesions represent a consecutive nonselected series.

The control group consists of nine patients without evidence of valvular or myocardial heart disease. They all had normal coronarograms. The mean age in this group was 47.3 years (range 36 to 58 years).

Twelve patients with predominant aortic stenosis had a mean age of 43.4 years (range 14 to 59 years). Average aortic valve area was  $0.68 \text{ cm}^2/\text{M}^2$  (range  $0.40$  to  $1.29 \text{ cm}^2/\text{M}^2$ ) and average peak systolic pressure gradient was  $78.3 \text{ mm Hg}$  (range  $40$  to  $120 \text{ mm Hg}$ ). Aortic root angiography was performed in all these patients and revealed additional aortic incompetence in eight patients estimated as  $1+$  (out of a maximum of  $3+$ ). No patients had additional mitral valve disease. The presence and severity of symptoms were assessed from the clinical records. We recorded NYHA functional class considering

From the Kerckhoff Clinic, Bad Nauheim, and from the Department of Cardiovascular Surgery, Justus Liebig University, Giessen, West Germany.

Received for publication Aug. 30, 1976.

Accepted for publication Dec. 10, 1976.

Reprint requests: F. Schwarz, M.D., 6350 Bad Nauheim, Kerckhoff Klinik, Benekestrasse 68, W. Germany.

0002-8703/78/0229-0146\$00.80/0 © 1978 The C.V.

typical symptoms associated with aortic valve disease, angina, syncope and dyspnea. Seven patients of this group were in Class II, four in Class III and one in Class IV. Selective coronary angiography was performed in all patients except the child of 14 years and showed coronary arteries without obstructions.

Twelve patients had predominant aortic regurgitation. Their mean age was 38 years (range 16 to 63 years). All patients had massive regurgitation scored as 3+ from aortic root angiography. Average aortic valve area in this group was  $2.19 \text{ cm}^2/\text{M}^2$  (range 1.41 to  $2.9 \text{ cm}^2/\text{M}^2$ ). Six patients had additional peak systolic pressure gradients between 6 and 20 mm Hg. Two patients had additional mild mitral incompetence without mitral stenosis. Five patients were in Class II and seven in Class III. In the six patients above 40 years of age, coronary angiography showed no abnormalities.

Two patients had mixed aortic valve lesions with massive aortic regurgitation of 3+ aortic valve areas of 1.15 and  $1.25 \text{ cm}^2/\text{M}^2$  and peak systolic pressure gradients of 48 and 50 mm Hg. Additional mild mitral incompetence was present in one patient. Both patients were in Class III and had coronary arteries without obstructions.

Pre and postoperative studies were performed in another series of six patients. Four of them had preoperatively predominant aortic stenosis with an average aortic valve area of  $0.58 \text{ cm}^2/\text{M}^2$  (range 0.42 to  $0.70 \text{ cm}^2/\text{M}^2$ ) and a peak systolic pressure gradient of 116 mm Hg (range 64 to 186 mm Hg). Mild additional (1+ out of a maximum of 3+) aortic regurgitation was found in two of these four patients. The remaining two patients had a massive aortic regurgitation of 3+ with aortic valve areas of 1.7 and  $2.3 \text{ cm}^2/\text{M}^2$  and peak systolic pressure gradients of 12 and 30 mm Hg. The postoperative evaluation was carried out  $92 \pm 13$  months (mean  $\pm$  SEM) after aortic valve replacement (Bjork Shiley prosthesis).

**2. Conduction of the study.** Heart rate, left atrial pressure, left ventricular pressure (8F Brockenbrough catheter, transeptal approach) and aortic pressure (8F pigtail catheter, femoral artery) were recorded before use of contrast material using Statham P23Db pressure transducers at the midchest position. Thereafter 50 ml Urografin 76 were injected into the left ventricle using the Brockenbrough catheter while cineangiograms were exposed at 48 frames/sec on

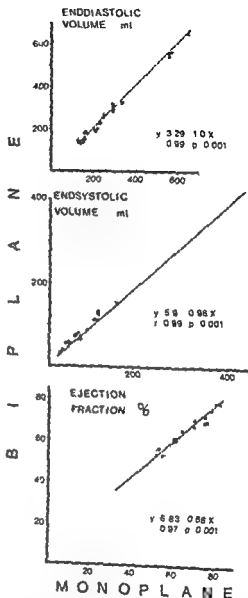


Fig 1 Comparison between end-diastolic volume and end-systolic volume and ejection fraction measured by single plane (monoplane) and biplane angiography.  $r$  = correlation coefficient.

a 35 mm film (RAO position). Simultaneously the ECG and the aortic pressure were recorded with a paper speed of 100 mm/sec on an oscillogram direct writing system. Ventriculography was repeated after a waiting period of at least 25 minutes during continuous infusion of  $0.3 \mu\text{g}/\text{kg}$  body weight/min isoproterenol. The Brockenbrough catheter was withdrawn into the left atrium and ventriculography was performed by injection into the atrium. Thereafter selective cinecoronangiography was performed using the Judkins technique.

**Table 1** Comparison of cardiac function before and during isoproterenol infusion between patients with predominant aortic stenosis and patients with predominant aortic regurgitation (both groups had comparable degrees of ventricular hypertrophy)

|                                 | LVMMI           | HR<br>(beats/min) | LVSP<br>(mm Hg) | AoPd<br>(mm Hg) | EDV<br>(ml/M <sup>2</sup> ) | EF<br>(%)      | VCF<br>(circumfer/sec) | MLAP<br>(mm Hg) | LVEDP<br>(mm Hg) | AVA<br>(cm <sup>2</sup> /M <sup>2</sup> ) |
|---------------------------------|-----------------|-------------------|-----------------|-----------------|-----------------------------|----------------|------------------------|-----------------|------------------|---|
| <b>Rest</b>                     |                 |                   |                 |                 |                             |                |                        |                 |                  |   |
| Aortic stenosis<br>(n = 11)     | 226.5<br>± 80.7 | 84.0<br>± 11.7    | 196.4<br>± 30.3 | 71.5<br>± 15.2  | 127.9<br>± 67.7             | 61.4<br>± 16.3 | 1.05<br>± 0.40         | 14.4<br>± 9.0   | 20.6<br>± 10.0   | 0.68<br>± 0.26                            |
| Aortic regurgitation<br>(n = 8) | 223.5<br>± 67.6 | 79.5<br>± 12.6    | 155.3<br>± 15.4 | 61.3<br>± 14.6  | 171.8<br>± 34.7             | 58.8<br>± 12.8 | 0.94<br>± 0.23         | 11.0<br>± 5.2   | 17.9<br>± 6.4    | 0.18<br>± 0.40                            |
| P value                         | ns              | ns                | <0.01           | ns              | ns                          | ns             | ns                     | ns              | ns               | <0.001                                    |
| <b>Isoproterenol</b>            |                 |                   |                 |                 |                             |                |                        |                 |                  |   |
| Aortic stenosis<br>(n = 11)     | 226.5<br>± 80.7 | 130.9<br>± 13.6   | 254.0<br>± 49.1 | 66.0<br>± 15.2  | 118.6<br>± 77.9             | 68.9<br>± 16.3 | 1.72<br>± 0.62         | 16.0<br>± 11.5  | 18.8<br>± 13.9   | 0.4<br>± 0.31                             |
| Aortic regurgitation<br>(n = 8) | 223.5<br>± 67.6 | 122.9<br>± 23.6   | 174.5<br>± 18.1 | 57.0<br>± 14.3  | 151.8<br>± 38.5             | 70.5<br>± 10.6 | 1.81<br>± 0.40         | 9.2<br>± 7.3    | 9.9<br>± 5.1     | 2.63<br>± 1.23                            |
| P value                         | ns              | ns                | <0.001          | ns              | ns                          | ns             | ns                     | ns              | ns               | <0.01                                     |

Abbreviations: LVMMI = left ventricular muscle mass index (Gm/M<sup>2</sup> of body surface area); HR = heart rate; LVSP = left ventricular systolic pressure; AoPd = diastolic aortic pressure; EDV = end-diastolic volume; EF = ejection fraction; VCF = mean fiber shortening rate; MLAP = mean left atrial pressure; LVEDP = left ventricular end diastolic pressure; AVA = aortic valve area.  
Data are mean values ± standard deviation.

**3 Angiographic methods** Quantitative ventriculography was done using a sphere calibration technique and the area length method<sup>1</sup> modified for the RAO position.<sup>2,3</sup> End diastolic and end systolic volumes were derived from the largest and smallest silhouettes of the left ventricle using the apex and the aortic root as reference points. Ventriculographic images selected for analysis were taken from the first four sinus beats following contrast material injection. Heart rate did not change more than 5 bpm during ventriculography as compared to heart rate measured during pressure recordings. All volume data were corrected according to the formula of Sandler and Dodge.<sup>4</sup> To assess ventricular function, ejection fraction was determined as stroke volume divided by end diastolic volume times 100 per cent. The minor equator (D) was calculated as  $D = 4 \text{ area} / \pi \times L$  where L is the long axis of the ventricle. The percentage shortening of minor equator was determined as end diastolic minus end systolic divided by end diastolic equator. Mean circumferential fiber shortening rate was calculated as percentage shortening of minor equator divided by ejection time as measured from the aortic pulse during ventriculography. Ventricular volumes were determined by single plane as well as biplane ventriculography in 25 patients in order to compare both methods. Left ventricular

wall thickness was measured in the RAO projection as proposed by Falsetti and colleagues.<sup>1</sup> Left ventricular mass was determined according to Rackley and associates.<sup>14</sup> Aortic valve area was calculated utilizing a modification of the Gorlin formula<sup>14</sup> after Bache and co-workers.<sup>15</sup> Aortic valve area =  $Q / 37 \sqrt{\text{PPSG} + 10}$  where Q = cardiac output divided by the systolic ejection period; PPSG = peak to peak left ventricular to aortic pressure gradient. Cardiac output was calculated as angiographic stroke volume times heart rate. Valve areas determined by this method were found to be greater than those reported by others using the Fick principle<sup>16,17</sup> but agree closely with values obtained by Lewis and colleagues<sup>18</sup> and by Kennedy<sup>19</sup> using the angiographic technique. We believe that this method is preferable because even in "pure" aortic stenosis we found frequently mild regurgitation during aortic root angiography. Statistical analysis was carried out using the Student t test and linear regression analysis.

## Results

Comparison of monoplane and biplane volumes for normal and enlarged ventricles showed an excellent correlation ( $r = 0.994$ ) for end diastolic volumes ranging from 134 to 645 ml (Fig 1). A similar correlation ( $r = 0.996$ ) was found for end

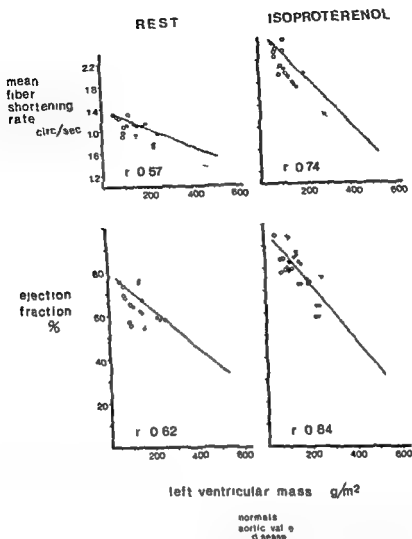


Fig 2 Correlation between left ventricular muscle mass and mean fiber shortening rate (upper panel) or ejection fraction (lower panel) during rest (left) and during isoproterenol infusion (right)  $r$  = correlation coefficient. The open circles represent values of normal patients; closed circles represent values for patients with aortic valve disease.

systolic volumes over the range of 26 to 425 ml and for ejection fractions ( $r = 0.973$ ) over a range of 34 to 84 per cent.

Eleven out of twelve patients with predominant aortic stenosis and 8 out of 12 patients with predominant aortic regurgitation were selected according to their left ventricular mass to achieve two groups with nearly identical and therefore comparable degree of hypertrophy (Table I). Left ventricular peak systolic pressure and aortic valve area were significantly different between both groups ( $p < 0.01$ ). Heart rate, diastolic aortic pressure, end diastolic volume, ejection fraction, mean fiber shortening rate, mean left atrial pressure, and left ventricular end diastolic

pressure were not significantly different ( $p > 0.05$ ) between both groups either at rest or during isoproterenol infusion.

It is therefore justified to correlate the ejection fraction and mean fiber shortening rate to the left ventricular muscle mass irrespective of the type of overload as shown in Fig 2. During rest the correlation for mean fiber shortening rate was poor ( $r = 0.57$ ,  $p < 0.001$ ) but improved during isoproterenol ( $r = 0.74$ ,  $p < 0.001$ ). Both these regression lines are significantly different ( $p < 0.01$ ). The relation between muscle mass and ejection fraction was poor at rest ( $r = 0.62$ ,  $p < 0.001$ ) but also improved considerably during isoproterenol ( $r = 0.84$ ,  $p < 0.001$ ).



Table II Left ventricular function in normal patients and in patients before and after aortic valve replacement under resting conditions and during isoproterenol stress

|  | LVMMI<br>*†     | HR<br>(beats/min) | LVSP<br>(mm Hg) | AoPd<br>(mm Hg) | FDV<br>(ml/M <sup>2</sup> ) | EF<br>(%)      | VCF<br>(circumfer/sec) | M(LAP<br>(mm Hg) | LVEDP<br>(mm Hg) | AVA<br>(cm <sup>2</sup> /M <sup>2</sup> ) |
|--|-----------------|-------------------|-----------------|-----------------|-----------------------------|----------------|------------------------|------------------|------------------|---|
| <i>Rest</i>                                      |                 |                   |                 |                 |                             |                |                        |                  |                  |   |
| Normals<br>(n = 9)                               | 87.3<br>± 22.6† | 72.0<br>± 10.2    | 125.8<br>± 11.3 | 71.6<br>± 9.3   | 91.9<br>± 26.9              | 68.1<br>± 7.9  | 1.19<br>± 0.18         | 9.1<br>± 2.8     | 10.4<br>± 4.5    | 1.68<br>± 0.46                            |
| Before aortic<br>valve<br>replacement<br>(n = 6) | 315.6<br>± 62.1 | 80.3<br>± 11.0    | 188.7<br>± 56.9 | 50.0<br>± 6.2   | 223.0<br>± 71.7             | 48.0<br>± 15.9 | 0.63<br>± 0.27         | 20.3<br>± 11.7   | 29.3<br>± 9.9    | 1.01<br>± 0.9                             |
| Before vs<br>Normals                             | <0.001          | n.s.              | <0.05           | <0.01           | <0.01                       | <0.01          | <0.001                 | <0.01            | <0.01            | n.s.                                      |
| After aortic<br>valve<br>replacement<br>(n = 6)  | 146.9<br>± 43.5 | 77.6<br>± 8.2     | 143.3<br>± 13.3 | 74.5<br>± 8.2   | 90.7<br>± 14.7              | 68.3<br>± 11.2 | 1.29<br>± 0.30         | 8.8<br>± 3.6     | 13.2<br>± 1.7    | 1.30<br>± 0.31                            |
| After vs<br>Before                               | <0.01           | n.s.              | n.s.            | <0.01           | <0.01                       | <0.01          | <0.01                  | <0.01            | <0.01            | n.s.                                      |
| After vs<br>Normals                              | <0.05           | n.s.              | <0.01           | n.s.            | n.s.                        | n.s.           | n.s.                   | n.s.             | n.s.             | n.s.                                      |
| <i>Isoproterenol</i>                             |                 |                   |                 |                 |                             |                |                        |                  |                  |   |
| Normals<br>(N = 9)                               | 87.3<br>± 22.6  | 142.0<br>± 11.9   | 128.8<br>± 16.1 | 67.6<br>± 9.4   | 74.1<br>± 21.3              | 85.0<br>± 5.4  | 2.43<br>± 0.10         | 4.2<br>± 1.3     | 6.1<br>± 2.9     | 2.31<br>± 0.48                            |
| After aortic<br>valve<br>replacement<br>(n = 6)  | 146.9<br>± 43.5 | 141.8<br>± 6.1    | 183.3<br>± 12.2 | 62.0<br>± 6.5   | 92.2<br>± 18.5              | 76.5<br>± 6.9  | 2.03<br>± 0.24         | 9.8<br>± 4.7     | 9.3<br>± 5.0     | 1.20<br>± 0.36                            |
| After vs<br>Normals                              | <0.05           | n.s.              | <0.001          | n.s.            | n.s.                        | <0.05          | <0.01                  | <0.01            | n.s.             | <0.001                                    |

Abbreviations as in Table I

†Data are mean values ± standard deviation

\*Left ventricular muscle mass index (LVMMI) measured in Gm/M<sup>2</sup> of body surface area

A poor but significant ( $r = 0.47$ ,  $p < 0.01$ ) inverse relation was found between left ventricular end diastolic pressure and ejection fraction at rest. This correlation however worsened during isoproterenol infusion ( $r = 0.44$ ,  $p < 0.05$ ). A similar inverse relation between mean left atrial pressure and ejection fraction was observed at rest ( $r = 0.56$ ,  $p < 0.001$ ) and improved during isoproterenol ( $r = 0.66$ ,  $p < 0.001$ ) suggesting that mean left atrial pressure roughly reflects pump function of the left ventricle in aortic valve disease.

Table II shows the results in patients before and nine months after aortic valve replacement as compared to the control group. Left ventricular muscle mass which was significantly elevated before surgery ( $p < 0.001$ ) decreased after valve replacement ( $p < 0.01$  if sets of paired observations were compared) but remained abnormally elevated ( $p < 0.05$ ). Resting values of

ejection fraction, mean fiber shortening rate, and mean left atrial pressure which were pathologic before surgery, normalized after valve replacement. Cardiac reserve tested during isoproterenol infusion after surgery revealed an abnormal response of ejection fraction, mean fiber shortening rate and mean left atrial pressure as compared to normal patients ( $p < 0.05$ ). Fig 3 indicates that the persisting hypertrophy after corrective surgery is associated with an incomplete restoration of cardiac reserve suggesting that the relation between mass and reserve remains valid after surgery.

#### Discussion

Some methodological problems need discussion. First of all it has to be considered that monoplane angiography may result in erroneous measurements of left ventricular volumes. Cohn and colleagues<sup>1</sup> found good agreement of monoplane

and biplane angiography in normal patients and in patients with coronary artery disease without evidence of asynergy. Our observation was that monoplane and biplane angiograms correlate excellently in ventricles with aortic valve disease without coronary artery disease (Fig 1). This is mainly due to the fact that ventricular geometry in aortic valve disease remains nearly normal. The ejection fraction and the mean circumferential fiber shortening rate<sup>20</sup> were used in this study to define left ventricular function at rest and during isoproterenol stress. Peterson and co-workers<sup>7</sup> compared isovolumic and ejection phase indices in normal and diseased hearts and found that in patients with diffuse myocardial involvement ejection phase contractile indices offer a preferable mode for assessing myocardial function. The ejection phase indices showed superior sensitivity for identifying normal and abnormal patients with minimal individual overlap whereas isovolumic indices although separating normal and diseased hearts showed considerable overlap of individual values. The ejection fraction measured at rest has prognostic significance in the surgical treatment of valvular heart disease since patients with depressed ejection fractions have a poorer short term prognosis than patient with normal ejection fractions.<sup>21</sup> It was further shown that the evaluation of the contractile reserve determined by the ejection fraction after postextrasystolic potentiation or during epinephrine infusion helped to establish a close relation between ventricular function and prognosis in patients with coronary artery disease.<sup>22</sup>

Isoproterenol as a beta stimulating drug enhances left ventricular performance in normal and diseased hearts.<sup>1, 2</sup> Quinones and colleagues described an augmentation of contractility as measured from an increase of mean circumferential fiber shortening rate of 58 per cent during isoproterenol infusion in normal individuals. Geha and associates found a significant increase of contractile behavior in normal and hypertrophied dog hearts. In the present study we used isoproterenol to evaluate cardiac reserve.<sup>23</sup>

Left ventricular function and reserve were not different between chronic pressure and chronic volume overload if patients with nearly identical left ventricular muscle masses are compared. Mehmel and co-workers using a similar approach found no differences of Vpm between two groups of patients with chronic pressure and volume

## ISOPROTERENOL

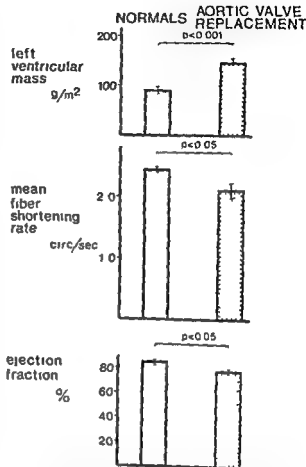


Fig 3 Left ventricular muscle mass and reserve function in normal patients and in patients after aortic valve replacement. Left ventricular muscle mass is still significantly increased nine months after surgery. Reserve function (mean fiber shortening rate and ejection fraction) is reduced in these hypertrophied hearts. The columns represent mean values  $\pm$  SEM.

overload but with comparable muscle masses. They concluded that in advanced hypertrophy contractility is reduced irrespective of the stimulating factor. Our results support this concept. Therefore we related left ventricular function to the degree of hypertrophy irrespective of the type of aortic valve lesion. Under control conditions this relation was poor probably due to the compensatory capacity of the hypertrophied ventricle<sup>2</sup> and the Frank-Starling mechanism.<sup>24</sup> When however the hypertrophied hearts were forced to mobilize their reserve a close inverse relationship between muscle mass and reserve force was found (Fig 2). Thus stress could demonstrate a depression of cardiac reserve when

**Table II** Left ventricular function in normal patients and in patients before and after aortic valve replacement under resting conditions and during isoproterenol stress

|  | LVMMI<br>†      | HR<br>(beats/min) | LVSP<br>(mm Hg) | AoPd<br>(mm Hg) | EDV<br>(ml/M <sup>2</sup> ) | EF<br>(%)      | VCF<br>(circumfer/sec) | MLAP<br>(mm Hg) | LVEDP<br>(mm Hg) | AVA<br>(cm <sup>2</sup> /M <sup>2</sup> ) |
|--|-----------------|-------------------|-----------------|-----------------|-----------------------------|----------------|------------------------|-----------------|------------------|---|
| <i>Rest</i>                                      |                 |                   |                 |                 |                             |                |                        |                 |                  |   |
| Normals<br>(n = 9)                               | 87.3<br>± 22.6† | 72.0<br>± 10.2    | 125.8<br>± 11.3 | 71.6<br>± 9.3   | 91.9<br>± 26.9              | 68.1<br>± 7.9  | 1.19<br>± 0.18         | 9.1<br>± 2.8    | 10.4<br>± 4.5    | 1.68<br>± 0.46                            |
| Before aortic<br>valve<br>replacement<br>(n = 6) | 315.6<br>± 62.1 | 80.3<br>± 11.0    | 188.7<br>± 56.9 | 55.0<br>± 6.2   | 223.0<br>± 71.7             | 48.0<br>± 15.9 | 0.63<br>± 0.27         | 25.3<br>± 11.7  | 29.3<br>± 9.9    | 1.0<br>± 0.9                              |
| Before vs<br>Normals                             | <0.001          | ns                | <0.05           | <0.01           | <0.01                       | <0.05          | <0.001                 | <0.05           | <0.01            | ns  |
| After aortic<br>valve<br>replacement<br>(n = 6)  | 146.9<br>± 43.5 | 77.6<br>± 8.2     | 143.3<br>± 13.3 | 74.5<br>± 8.2   | 95.7<br>± 14.7              | 68.3<br>± 11.2 | 1.29<br>± 0.39         | 8.8<br>± 3.5    | 13.2<br>± 1.7    | 1.30<br>± 0.31                            |
| After vs<br>Before                               | <0.01           | ns                | ns              | <0.01           | <0.01                       | <0.05          | <0.05                  | <0.05           | <0.01            | ns  |
| After vs<br>Normals                              | <0.05           | ns                | <0.05           | ns              | ns                          | ns             | ns                     | ns              | ns               | ns  |
| <i>Isoproterenol</i>                             |                 |                   |                 |                 |                             |                |                        |                 |                  |   |
| Normals<br>(N = 9)                               | 87.3<br>± 22.6  | 142.0<br>± 11.9   | 128.8<br>± 16.1 | 67.6<br>± 9.4   | 74.1<br>± 21.2              | 85.0<br>± 5.4  | 2.43<br>± 0.10         | 4.2<br>± 1.3    | 6.1<br>± 2.9     | 2.3†<br>± 0.48                            |
| After aortic<br>valve<br>replacement<br>(n = 6)  | 146.9<br>± 43.5 | 144.8<br>± 6.1    | 183.3<br>± 12.2 | 62.0<br>± 6.5   | 92.2<br>± 18.5              | 76.5<br>± 6.9  | 2.03<br>± 0.24         | 9.8<br>± 4.7    | 9.3<br>± 5.0     | 1.70<br>± 0.38                            |
| After vs<br>Normals                              | <0.05           | ns                | <0.001          | ns              | ns                          | <0.05          | <0.01                  | <0.05           | ns               | <0.001                                    |

Abbreviations as in Table I

†Data are mean values ± standard deviation

‡Left ventricular muscle mass index (LVMMI) measured in Gm/M<sup>2</sup> of body surface area

A poor but significant ( $r = 0.47$ ,  $p < 0.01$ ) inverse relation was found between left ventricular end diastolic pressure and ejection fraction at rest. This correlation however worsened during isoproterenol infusion ( $r = 0.44$ ,  $p < 0.05$ ). A similar inverse relation between mean left atrial pressure and ejection fraction was observed at rest ( $r = 0.56$ ,  $p < 0.001$ ) and improved during isoproterenol ( $r = 0.66$ ,  $p < 0.001$ ) suggesting that mean left atrial pressure roughly reflects pump function of the left ventricle in aortic valve disease.

Table II shows the results in patients before and nine months after aortic valve replacement as compared to the control group. Left ventricular muscle mass which was significantly elevated before surgery ( $p < 0.001$ ) decreased after valve replacement ( $p < 0.01$ , if sets of paired observations were compared) but remained abnormally elevated ( $p < 0.05$ ). Resting values of

ejection fraction, mean fiber shortening rate and mean left atrial pressure which were pathologic before surgery, normalized after valve replacement. Cardiac reserve tested during isoproterenol infusion after surgery revealed an abnormal response of ejection fraction, mean fiber shortening rate and mean left atrial pressure as compared to normal patients ( $p < 0.05$ ). Fig 3 indicates that the persisting hypertrophy after corrective surgery is associated with an incomplete restoration of cardiac reserve suggesting that the relation between mass and reserve remains valid after surgery.

## Discussion

Some methodological problems need discussion first of all it has to be considered that monoplane angiography may result in erroneous measurements of left ventricular volumes. Cohn and colleagues<sup>10</sup> found good agreement of monoplane

- incompetence prognostic implications *Circulation* 49 and 50 (Suppl III) III 41 1974
2. Bolooki H and Kaiser G Significance of cardiac function in surgical management of patients with valvular heart disease *Am J Cardiol* 37 319 1976
3. Kennedy J W Twiss R D Blackmon J R and Dodge H T Quantitative angiocardiography III Relationships of left ventricular pressure volume and mass in aortic valve disease *Circulation* 38 838 1968
4. Lewis R P Branton J H and Griswold H H Exercise hemodynamics in aortic regurgitation *Am Heart J* 80 171 1970
5. Mehmel H C Mazzoni S and Karyenbuehl H P Contractility of the hypertrophied human left ventricle in chronic pressure and volume overload *Am Heart J* 90 936 1975
6. Bolen J L Holloway E L Zener J C Harrison D C and Aldermann H L Evaluation of left ventricular function in patients with aortic regurgitation using after load stress *Circulation* 53 137 1976
7. Lee S J K Jonsson B Bevegard S Karlof J and Astrom H Hemodynamic changes at rest and during exercise in patients with aortic stenosis of varying severity *Am Heart J* 79 318 1970
8. Sandler H and Dodge H T The use of single plane angiocardiograms for the calculation of left ventricular volume in man *Am Heart J* 75 325 1968
9. Greene D G Carlisle H Grant C and Bunnell I L Estimation of left ventricular volume by one plane cineangiography *Circulation* 35 61 1967
10. Cohn P F Gorlin R Adams D F Chahine R A Yokonas M S and Herman M V Comparison of biplane and single plane ventriculograms in patients with coronary artery disease *Am J Cardiol* 33 1 1974
11. Hamby R I Aintablian A Wosoff B G and Hartstein M L Response of the left ventricle in coronary artery disease to postextrasystolic potentiation *Circulation* 51 4 8 1975
12. Falsetti H L Mates R E Grant C Greene D G and Bunnell J L Left ventricular wall stress calculated from one plane cineangiography *Circ Res* 26 71 1970
13. Rackley C E Dodge H T Coble Y D and Hay R E A method for determining left ventricular mass in man *Circulation* 29 666 1964
14. Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve other cardiac valves and central circulatory shunts *Am Heart J* 41 1 1951
15. Bache R J Jorgensen C R and Wang Y Simplified estimation of aortic valve area *Br Heart J* 34 408 1972
16. Liedtke A J Gentzler R D Babb J H Hunter A H and Gault J H Determinants of cardiac performance in severe aortic stenosis *Chest* 69 197 1976
17. Fallen E L Elliott W C and Gorlin R Mechanism of angina in aortic stenosis *Circulation* 36 480 1967
18. Lewis A B Heymann M A Stanger P Hoffmann J I E and Rudolph A M Evaluation of subendocardial ischemia in valvular aortic stenosis in children *Circulation* 49 978 1974
19. Dodge H T Lord J D and Sandler H Cardiovascular effects of isoproterenol in normal subjects and in subjects with congestive heart failure *Am Heart J* 60 94 1960
20. Moss A J and Quivers W W Use of isoproterenol in the evaluation of aortic and pulmonic stenosis *Am J Cardiol* 12 734 1963
21. Brodsky S J Krovetz L J and Schiebler H L Assessment of severity of isolated valvular pulmonic stenosis using isoproterenol *Am Heart J* 80 660 1970
22. Neal W A Lucas R V Rao S and Moller J H Comparison of the hemodynamic effects of exercise and isoproterenol infusion in patients with pulmonary valvular stenosis *Circulation* 49 948 1974
23. Geha A S Mahk A B Abe T and O Kane H O Response of the hypertrophied heart to stress *Surgery* 74 976 1973
24. Ross J Jr Adaptations of the left ventricle to chronic volume overload *Circ Res* 34 and 35 (Suppl II) 55 1974
25. Mason D T Regulation of cardiac performance in clinical heart disease *Am J Cardiol* 32 437 1973
26. Spann J F Buccino H A Sonnenblick E H and Braunwald E Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure *Circ Res* 21 341 1967
27. Gunning J F Cooper G, Harrison C H and Coleman H N Myocardial oxygen consumption in experimental hypertrophy and congestive heart failure due to pressure overload *Am J Cardiol* 32 47 1973
28. Strauer B E and Taubert M Evidence for an inefficient energy utilization in cardiac hypertrophy. Studies on the isolated human ventricular myocardium *Klin. Wochenschr* 51 372 1973
29. Marchetti G V Merlo L Nosedo V and Visoli O Myocardial blood flow in experimental cardiac hypertrophy in dogs *Cardiovasc Res* 7 519 1973
30. Karlner J S Gault J H Eckberg D Mullins C B and Ross J Jr Mean velocity of fiber shortening A simplified measure of left ventricular myocardial contractility *Circulation* 44 373 1971
31. Peterson K L Skloven D Ludbrook P Uther J B and Ross J Jr Comparison of isovolumic and ejection phase indices of myocardial performance in man *Circulation* 49 1088 1974
32. Cohn P F Gorlin R Cohn L H and Collins J J Jr Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary and valvular heart disease *Am J Cardiol* 34 136 1974
33. Cohn P F Gorlin R Herman M V Sonnenblick E H Horn H R Cohn L H and Collins J J Jr Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction *Circulation* 51 414 1975
34. Quinones M A Gaasch W H and Alexander J K Influence of acute changes in preload afterload contractile state and heart rate on ejection and isovolumic indices of myocardial contractility in man *Circulation* 53 993 1976
35. Kennedy J W Twiss R D Blackmon J R and Merendino K A Hemodynamic studies one year after homograft aortic valve replacement *Circulation* 37 and 38 (Suppl I) II 110 1968
36. Papadimitrou J M Hopkins H E and Taylor R R Regression of left ventricular dilation and hypertrophy after removal of volume overload Morphological and ultrastructural study *Circ Res* 35 127 1974

differences at rest were only slight or absent. This suggests that changes in the development of hypertrophy occur which may be responsible for the loss of contractile reserve in these hearts. Spann and colleagues<sup>6</sup> found in hypertrophied isolated cat papillary muscles that hypertrophy in the absence of cardiac failure was associated with a depression of contractility per unit of myocardium. Gunning and associates<sup>7</sup> concluded from experiments in hypertrophied cat papillary muscles due to pressure overload that the depressed contractility is associated with an augmented myocardial oxygen consumption. Strauer and Tauchert<sup>28</sup> found an inefficient energy utilization in the isolated hypertrophied human ventricular myocardium. These results point out that biochemical correlates at the cellular level may be involved in the process leading to mechanical dysfunction in advanced cardiac hypertrophy. A second mechanism may be responsible for the decline of contractile reserve with increasing severity of hypertrophy. Marchetti and colleagues<sup>29</sup> described a reduced coronary reserve in dogs with moderate hypertrophy due to volume overload. This suggests that myocardial perfusion may also be responsible for the impairment of contractile reserve in hypertrophied hearts.

Comparison of pre and postoperative evaluation in six patients with advanced aortic valve disease and severe left ventricular hypertrophy shows a drastic reduction of left ventricular muscle mass after surgery to 53 per cent of the preoperative value. This regression, however, is incomplete if compared to normal patients. An incomplete regression of left ventricular hypertrophy was also observed by Kennedy and co-workers<sup>15</sup> in patients with homograft aortic valve replacement and by Papadimitriou and associates<sup>30</sup> in dogs after closure of a large aortocaval fistula. Cardiac function at rest which was severely compromised before surgery, normalized completely in our patients after successful correction of overload. Contractile reserve, however, was still depressed. This demonstrates that after correction of overload by aortic valve replacement the hearts shifted upwards and to the left on the mass function curve shown in Fig. 2 indicating improved cardiac performance. It has to be considered, however, that Bjork-Shiley prostheses produce an increased afterload which may be responsible for the incomplete regression

of left ventricular hypertrophy and the incomplete restoration of contractile reserve.

### Summary

The relations between left ventricular (LV) hypertrophy as estimated by LV mass and LV function and between LV hypertrophy and cardiac reserve were evaluated in 26 patients with aortic valve disease and in nine normal patients who served as controls. Ejection fraction (EF) and mean circumferential fiber shortening rate (VCF) served as indices of LV function. Reserve force of the left ventricle was tested by ventriculography during infusion of 0.3 µg/Kg body weight/min isoproterenol. EF and VCF were not significantly different ( $p > 0.05$ ) either at rest or during isoproterenol infusion if patients with aortic stenosis were compared to patients with aortic regurgitation having comparable LV masses. Therefore we correlated the EF and VCF to the LV mass of all patients irrespective of the type of aortic valve lesion. Poor but significant inverse correlations were found at rest between LV mass and EF ( $r = 0.62$ ) and between LV mass and VCF ( $r = 0.57$ ). These correlations improved considerably during isoproterenol:  $r = 0.84$  for EF and  $r = 0.74$  for VCF.

LV function was evaluated in another six patients with aortic valve disease before and nine months after successful aortic valve replacement by Bjork-Shiley prostheses. LV mass before surgery was 3.6 times control and decreased after surgery to 1.7 times control ( $p < 0.01$ ) which is still significantly elevated ( $p < 0.05$ ). EF and VCF which were depressed before surgery ( $p < 0.05$ ,  $p < 0.001$ ) normalized after surgery ( $p > 0.05$ ) but were reduced during isoproterenol infusion if compared to controls ( $p < 0.05$ ). Thus stress ventriculography in aortic valve disease could demonstrate a linear decrease of cardiac reserve with increasing severity of hypertrophy when resting function was normal or depressed only slightly. Regression of hypertrophy was incomplete 9 months after correction of overload and LV function which was depressed before surgery normalized at rest but was impaired during stress suggesting that cardiac reserve was not fully restored.

### REFERENCES

1. Bailey M. T., Field E. J. and Baxley W. A. Left ventricular function prior to surgery for aortic valve

but one case. Again these 14 patients were classified into one group.

It became apparent from the study of the clinical and pathological findings that the clinical features and hemodynamic alterations in each group were determined mainly by the function of the tricuspid valve as will be described later. In addition, given the fact that most patients with Ebstein's anomaly probably have some degree of tricuspid malfunction, each of the three groups was termed as Tricuspid Stenosis Dominant Type, Tricuspid Insufficiency Dominant Type and Mild Type respectively.

#### 1. Tricuspid Stenosis Dominant Type (cases No. 1 to 8, Table I)

**Clinical features.** The most consistent symptoms in this group were exertional dyspnea and palpitation, which were observed in five patients (cases No. 2, 3, 4, 7, and 8). Bouts of paroxysmal tachycardia were present in two (cases No. 1 and 8) and hypoxic spells in two (cases No. 2 and 5). Three patients showed severe cyanosis and five showed moderate cyanosis.

**Radiology.** A typical radiologic cardiac silhouette described as being box-like or balloon-shaped with a narrow pedicle was present in four patients (cases No. 2, 3, 4, and 8). This contour was formed mostly by the enlarged right atrium, which caused the bulging right border and ballooning of the right ventricular outflow tract, which formed the protrusion of the left upper border. Cardiomegaly was present in all but one patient, and the enlargement was estimated to be mild in four and moderate in three. Pulmonary vascularity was judged to be decreased in all.

**Right heart catheterization.** This study was performed on seven patients (Table IV). The right atrial A wave ranged from 8 to 11 mm Hg and the V wave ranged 8 to 10 mm Hg. The right ventricular systolic pressure ranged from 19 to 35 mm Hg and the end diastolic pressure ranged from 4 to 10 mm Hg. Five patients had a significant diastolic pressure gradient across the tricuspid valve. A right to left shunt at the atrial level was noted in five patients; two of these being demonstrated as having a left to right shunt also and one of them had a ventricular septal defect (case No. 7).

**Angiocardiography.** This study was performed on seven patients and adequate films were obtained in all. In all patients, the proximal chamber (the atrialized right ventricle) situated

**Table I. Clinical findings in patients of Tricuspid Stenosis Dominant Type.**

| Case No. | Age (yr) | Sex | NYHA class | Cyanosis | CTR (per cent) | Double ball sign | Surgery    | Autopsy |
|----------|----------|-----|------------|----------|----------------|------------------|------------|---------|
| 1        | 1        | M   | III        | +++      | III            | +                | palliative | —       |
| 2        | 7        | F   | III        | +++      | 6              | +                | TVR        | —       |
| 3        | 8        | F   | II         | ++       | 61             | +                | TVR        | —       |
| 4        | 19       | M   | III        | ++       | 70             | +                | —          | —       |
| 5        | 14       | M   | III        | ++       | 60             | +                | palliative | +       |
| 6        | 15       | F   | II         | ++       | 4              | +                | TVR        | +       |
| 7        | 22       | F   | III        | ++       | 63             | +                | TVR        | +       |
| 8        | 31       | F   | III        | +++      | 70             | +                | TVR        | —       |

CTR = cardiothoracic ratio; TVR = tricuspid valvular replacement = unknown.

between the right atrium and the distal chamber (the functioning right ventricle) was confirmed as being present. In four patients, contraction of the proximal chamber at the same time as the ventricular systole was noted, but in three patients (cases No. 1, 2, and 4) this chamber showed little contraction. The proximal chamber could be distinguished from the distal chamber by the notch toward the cardiac apex, indicating the displaced attachment of the tricuspid valve (Fig 1), or by the different concentrations of the contrast medium in these two chambers (Fig 3). In two patients (cases No. 1 and 6) in which the contrast medium was injected into the distal chamber, the proximal chamber surrounded by the parachute-like deformed tricuspid valve was not opacified and this portion appeared as a shadow defect in the right ventricle like an intraventricular tumor (Fig 2).

At peak diastole, the superior aspect of the infundibulum rose above the superior aspect of the pulmonary trunk, and this phenomenon became manifest in the frontal view as a ball-like density within another round density area. This sign was initially termed as a "double ball sign" by Elliot and Hartmann and was noted in all patients of the Tricuspid Stenosis Dominant Type.

**Anatomical findings.** Detailed anatomical findings were obtained in 4 patients (cases No. 1, 5, 6, and 7). In these, the anomaly was not simply a downward displacement of the attachment of the tricuspid valve, but it was also an abnormality of the entire tricuspid valvular apparatus and of the architecture of the right ventricle. In

# Clinical classification of Ebstein's anomaly

Shunsuke Takayasu MD

Yoshio Obunai MD

Souji Konno MD\*

Tokyo Japan

Since the first description by Ebstein in 1866<sup>1</sup> several hundred cases have been reported and the anomaly has attracted much attention through its broad clinical spectrum.

In this anomaly there is a variety of symptoms ranging from severe cyanosis, congestive heart failure and death in infancy to no cyanosis in patients who lived till the age of 79 years without any symptoms. In most previous studies, however, these patients have been classified simply into severe or mild cases according to their clinical features. In 1971 Bialostozky and colleagues<sup>2</sup> reported a review of 65 cases, and classified the patients into four groups according to their clinical findings and course.

The purpose of this paper is to present three types of classifications of 26 patients with Ebstein's anomaly according to their clinical features, radiologic findings, hemodynamic data and anatomical findings which were observed on surgery or autopsy and to consider the hemodynamic alterations in each type.

## Materials and methods

The 26 patients (12 males and 14 females) ranged in age from one to 51 years. Routine chest x-ray films were obtained in all patients. Right heart catheterization and selective angiocardiology were performed in 24 patients. Surgery was performed in 11 patients and autopsies were done in six patients, of which five were postoperative.

From the Heart Institute of Japan, Tokyo Women's Medical College, Tokyo, Japan.

Received for publication Sept. 5, 1976.

Accepted for publication Nov. 8, 1976.

Reprint request: Shunsuke Takayasu, MD, Department of Cardiovascular Surgery, The Kanto Tei Jun Ho Bldg, 5-9-2 Higashi-gotanda, Shinagawa, Tokyo, Japan.

\*Professor of Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women's Medical College.

The diagnoses of the other 14 patients were confirmed by clinical findings and angiocardiology.

## Clinical classification

In four out of 9 patients in whom the detailed anatomical findings were obtained, the tricuspid leaflets showed a great degree of deformity and the small tricuspid orifice was observed (cases No. 1, 5, 6 and 7). These patients were in a functional capacity Class II or III of NYHA, and they showed a moderate to severe cyanosis and a cardiomegaly. The cardiomegaly was estimated to be mild (cardiothoracic ratio greater than 56 per cent) or moderate (cardiothoracic ratio greater than 66 per cent) except for one patient who showed a normal sized heart. In two patients, right heart catheterization revealed a pressure gradient across the tricuspid valve and in three patients the 'double ball sign' on angiocardiology was present. The clinical findings of the four other patients (cases No. 2, 3, 4 and 8) were judged to be similar to these four patients and therefore these eight patients were grouped together.

All the patients with severe cardiomegaly (cardiothoracic ratio greater than 76 per cent) showed a mild to moderate cyanosis (cases No. 9 to 12). In three patients in whom right heart catheterization was performed, a tall and wide V wave of the right atrium was noted and on angiocardiology the double ball sign was present. An incompetent tricuspid valve was found in three patients at surgery or autopsy. These four patients were thought to resemble each other.

Of the remaining 14 patients, 11 were asymptomatic and three showed mild cyanosis, and all of them were in functional Class I or II. The chest roentgenogram revealed a mild to moderate cardiomegaly and the double ball sign was absent in all.

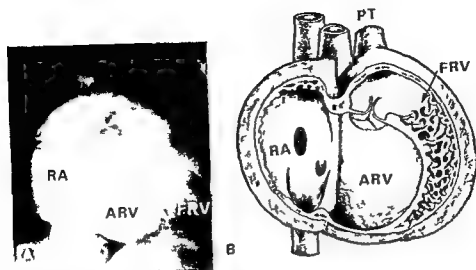


Fig 3 Frontal angiocardiogram in ventricular systole (A) and anatomical findings (B) of the patient of the Tricuspid Stenosis Dominant Type (case No 7) RA = right atrium ARV = atrialized right ventricle (proximal chamber) FRV = functioning right ventricle (distal chamber) PT = pulmonary trunk

The size of the distal chamber in three patients (cases No 5, 6 and 7) was less than that of the definitive right ventricle in a normal person. The right atrium was mildly enlarged and the aortic valve had a tendency to be prominent in all patients. One patient (case No 7) had a ventricular septal defect.

#### 2 Tricuspid Insufficiency Dominant Type (cases No 9 to 12 Table II)

**Clinical features** Two patients (cases No 9 and 10) were in Functional Class I and one patient (case No 11) showed a long stable course with only mild exertional dyspnea despite the markedly enlarged heart. Case No 12 was a 51 year old woman in whom cardiomegaly was first noted in her childhood and she remained asymptomatic until she had frequent bouts of tachycardia occurring at age 23. By the age of 41 she was first detected to be cyanotic and to have a severe cardiomegaly of 83 per cent. The patient died from congestive heart failure at age 51. Cyanosis was found to be mild in three cases and moderate in one.

**Radiology** Box-like severe cardiomegaly was observed in all patients (Fig 4). One patient (case No 10) showed a rapid progress of cardiomegaly from 74 to 84 per cent during the two years prior to surgery. On the other hand in two patients (cases No 11 and 12) the cardiomegaly remained unchanged for a long time. Pulmonary vascularity was considered to be normal in all patients.

Table II Clinical findings in patients of Tricuspid Insufficiency Dominant Type

| Case no | Age (yr) | Sex | NYHA class | Cyanosis | CTR (per cent) | Double ball sign | Surgery | Autopsy |
|---------|----------|-----|------------|----------|----------------|------------------|---------|---------|
| 9       | 7        | M   | I          | +        | 81             | +                | TVR     | +       |
| 10      | 8        | M   | I          | +        | 81             | +                | TVR     | -       |
| 11      | 49       | M   | II         | +        | 77             | +                | -       | -       |
| 12      | 51       | F   | III        | ++       | 93             | ?                | -       | +       |

CTR = cardiothoracic ratio TVR = tricuspid valvular replacement ? = unknown.

**Right heart catheterization (Table IV)** The most characteristic finding was the presence of a giant V wave of the right atrium which indicated severe tricuspid insufficiency ranging from 11 to 17 mm Hg. The right atrial mean pressure was equal to that of the right ventricle in two patients (cases No 9 and 10). The right atrial A wave ranged from 5 to 12 mm Hg and the right ventricular end diastolic pressure from 8 to 10 mm Hg. A diastolic pressure gradient across the tricuspid valve was noted in one patient.

**Angiocardiography** This study was performed on three patients. The proximal chamber could not be distinguished in two (cases No 9 and 10) because of the absence of the notch indicating the displaced attachment of the tricuspid valve. In one patient (case No 11) the proximal chamber was distinguished from the distal chamber by the



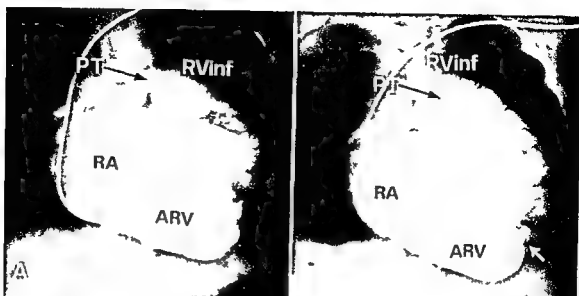


Fig 1 Frontal angiocardiogram of the patient of the Tricuspid Stenosis Dominant Type (case No. 2) in ventricular systole (A) and in diastole (B). Arrow indicates the demarcating notch. The double ball sign is shown in (B). RA = right atrium, ARV = atrialized right ventricle (proximal chamber), RVinf = right ventricular infundibulum, PT = pulmonary trunk.

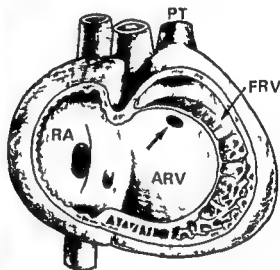


Fig 2 Frontal angiocardiogram in ventricular systole (A) and anatomical findings (B) of the patient of the Tricuspid Stenosis Dominant Type (case No. 6). The atrialized right ventricle appears as a shadow defect in the right ventricle. Arrow depicts a small opening in the parachute-like deformed tricuspid valve. FRV = functioning right ventricle (distal chamber), RA = right atrium, ARV = atrialized right ventricle (proximal chamber), PT = pulmonary trunk.

one patient (case No. 1) the base of the anterior leaflet was completely anchored on the original right atrioventricular orifice and in the other three patients the entire attachment of the three leaflets was displaced downward into the right ventricle. However, the tricuspid valve remained anchored on the pars membranacea in all of the patients.<sup>1</sup>

In three patients (cases No. 1, 5, and 6) the three leaflets were fused to each other to form a parachute with a small opening measuring 8 to 10 mm in diameter. In one of them (case No. 6) the

parachute was connected to the inner surface of the wall of the right ventricle by numerous intussusceptive fibers (Fig. 2). In another patient (case No. 5) the attachment of the tricuspid valve was deviated so far that the leaflets were just below the pulmonary valve, resulting in the distal chamber consisting of only a small cone. In case No. 7 the attachment of the three cusps extended downward to the narrow ring formed by the crista supraventricularis, parietal band, and the abnormally developed crista septomarginalis (Fig. 3).



Fig 5 Frontal angiocardigram in entricular systole (A) and in diastole (B) of the patient of the Tricuspid Insufficiency Dominant Type (case No 10). The right atrium and the right ventricle are markedly enlarged. The superior aspect of the right ventricular infundibulum rises above the superior aspect of the pulmonary trunk in diastole and thus appears in (B) as a dense opaque ball within a ball ("double ball sign"). RA = right atrium, RVinf = right ventricular infundibulum.

## Discussion

It is generally accepted that the fundamental hemodynamic alterations in Ebstein's anomaly lie in the proximal chamber.<sup>8</sup> The proximal chamber distends during the atrial contraction and reduces the amount of blood reaching the distal chamber and during the ventricular systole it contracts and forces the blood back into the right atrium. Thus filling of the right ventricle is impaired and the pulmonary flow is reduced and cyanosis is produced by the right to left shunt through the atrial septal defect.

These hemodynamic alterations were observed by angiocardigraphy in the patients reported here. The proximal chamber was noted in 20 patients and this portion contracted at the same time as the distal chamber in 17 patients but in three patients of the Tricuspid Stenosis Dominant Type little contraction was shown. It was of interest that even in the asymptomatic and acyanotic patients a large amount of blood was forced back into the right atrium by the contraction of the proximal chamber. There was no significant difference in the size of the proximal chamber between the severe patients of the Tricuspid Stenosis Dominant Type and the patients of the Mild Type.

It is thought that the hemodynamic alterations of the patients with Ebstein's anomaly have a



Fig 6 Specimen of the opened heart of the patient of the Tricuspid Insufficiency Dominant Type (case No 12) viewed from the right ventricular outflow tract. Arrow indicates the large defect on the posterior and septal leaflet. AL = anterior leaflet, APM = anterior papillary muscle, ARV = atrialized right ventricle (proximal chamber), FRV = functioning right ventricle (distal chamber), PT = pulmonary trunk.



Fig 4 Frontal chest roentgenogram of the patient of the Tricuspid Insufficiency Dominant Type (case No. 9) demonstrating box like severe cardiomegaly

different density of the contrast medium. Marked dilatation of the right atrium and the right ventricle was observed in all patients. The double ball sign was demonstrated in all and the volume change of the infundibulum was very large (Fig 5).

**Anatomical findings** Anatomical findings were obtained in three patients. In two patients (cases No. 9 and 10) each of the three leaflets was identifiable and showed a marked atrophy and in case No. 12 a large defect in the septal and posterior leaflet was found (Fig 6). It appeared obvious that there was severe tricuspid insufficiency in these patients.

The anterior leaflet arose from the normal orifice in all cases. There was a marked dilatation of the right atrium and of the distal portion of the right ventricle. An atrial septal defect was present in two patients (cases No. 9 and 10).

### 3. Mild Type (cases No. 13 to 26 Table III)

**Clinical features** Symptoms were present in eight of 14 patients of this type and were mild in all. The most common symptoms were exertional dyspnea present in six patients (cases No. 13, 15, 17, 19, 24 and 26). Bouts of paroxysmal tachycardia occurred in four and easy fatigability of precordial pain was noted in two (cases No. 24 and 25). Mild congestive heart failure was noted

in one patient (case No. 13) in whom a large left to right shunt at the atrial level was detected. Nine patients were in Functional Class I and the remaining five were in Class II.

Eleven patients had no cyanosis and of these five had no symptoms at all. Cyanosis was mild in three other patients. Hypoxic spells or squatting were not noted in any of the patients.

**Radiology** Cardiomegaly was present in all except one case. Seven patients showed a mild cardiomegaly and six showed a moderate one. A box like heart was present in four patients (cases No. 14, 17, 21, and 26). Pulmonary vascularity was considered to be normal in all but one (case No. 13) in whom it was increased.

**Right heart catheterization** (Table IV) This study was performed in all patients of this type. The right atrial A wave ranged from 4 to 13 mm Hg, the V wave ranged from 6 to 17 mm Hg, the right ventricular systolic pressure ranged from 20 to 34 mm Hg and the end diastolic pressure of the right ventricle ranged from 2 to 13 mm Hg. A diastolic pressure gradient across the tricuspid valve was demonstrated in two patients. The left to right shunt was detected in three patients and the right to left shunt in one patient.

**Angiocardiography** Detailed findings were obtained in all of the patients of this type. The proximal chamber was distinguished clearly in 12 patients and in all of these patients it showed a good contraction in accordance with that of the distal chamber. The large anterior leaflet was shown as a concavo convex movement in three patients (cases No. 16, 17 and 19 Fig 7). The double ball sign was absent in all but one (case No. 14).

**Anatomical findings** In two patients surgery was performed and anatomical findings were obtained. In case No. 13 each of the three leaflets of the tricuspid valve was identified with the large anterior leaflet arising from the original atrioventricular orifice. No tricuspid stenosis was observed and no insufficiency was demonstrated by the normal saline injection into the distal chamber during surgery. In case No. 10 the septal and posterior leaflets were atrophied and the large anterior leaflet which was attached to the original orifice seemed to compensate for the valvular function of the atrophied two leaflets. In these anatomical findings the architecture of the right ventricle was almost normal. Atrial septal defect was found in two patients.



Fig 7 Frontal angiocardiogram in ventricular systole (A) and in diastole (B) of the patient of the Mild Type (case No 17). Arrow indicates the concavo-convex movement of the large anterior leaflet of the tricuspid valve. The double ball sign is not observable. RA = right atrium. ARV = atrialized right ventricle (proximal chamber). FRV = functioning right ventricle (distal chamber).

an adequate sized distal chamber a sufficient output from the right ventricle should be maintained in spite of the presence of the proximal chamber. One patient of the Mild Type (case No 13) had congestive heart failure and it was thought to be due to the large left to right shunt. This was deduced from the disappearance of cardiac failure following the closure of the atrial septal defect. This patient might be an exceptional example of the Mild Type because the large left to right shunt is rare in Ebstein's anomaly.

The wide spectrum in Ebstein's anomaly together with the lack of longer follow up studies has resulted in a few reports about its natural history. Mahous and Vander Veer<sup>6</sup> estimated the life expectancy of Ebstein's anomaly to be 37 years from 219 cases reported throughout the world including six cases of their own. By contrast Kumar and associates<sup>7</sup> estimated median survival period to be 13 years from the 55 patients of his study. This marked difference seems to be attributed to the fact that in Kumar and colleagues' study many cases under one year of age were included. Concerning natural death by Ebstein's anomaly, Watson stated in an international co-operative study of 505 cases that after an initially high mortality rate of 45.7 per cent from congestive heart failure during the first year of life the mortality settles to an average of 12.4 per cent which is scattered fairly uniformly throughout childhood and adolescence.

According to Bialostzky and colleagues' classification Group I was comprised of asymptomatic

patients. Group II of symptomatic patients with no progression of clinical indexes. Group III of patients with marked symptoms as well as steady deterioration and Group IV of severely disabled patients. It is likely that the patients classified as Mild Type in this report correspond to patients of their Group I or II and that the patients of the Tricuspid Stenosis Dominant Type and the Tricuspid Insufficiency Dominant Type would be included in their Group III or IV.

The development of congestive heart failure and increasing cyanosis are grave prognostic signs. The prognosis of the patients of the Tricuspid Stenosis Dominant Type is thought to be poor due to their grave clinical features and the oldest patient of this series showed severe cyanosis and exercise limitation at age 26.

In patients of the Tricuspid Insufficiency Dominant Type congestive heart failure may develop especially in a patient such as case No 11 in whom cardiomegaly increased rapidly in a short time. However care must be taken with this type because there are a number of patients with significant cardiac enlargement and a long stable course as in case No 11. Case No 12 seems likely to be an exaggerated example of this type. She showed mild symptoms till age 40 even though there was severe cardiomegaly.

It would be interesting to know the prognosis of the patients of the Mild Type. In studying several reports of other investigators it is apparent that patients in class I or II of NYHA are most common<sup>3</sup> and even in this study cases of the

Table III Clinical findings in patients of Mild Type

| Case no | Age (yr) | Sex | NYHA class | Cyanosis | CTR (per cent) | Double ball sign | Surgery  | Autopsy |
|---------|----------|-----|------------|----------|----------------|------------------|----------|---------|
| 13      | 3        | F   | II         | -        | 70             | -                | ASD clos | -       |
| 14      | 4        | F   | I          | -        | 71             | +                | -        | -       |
| 15      | 7        | F   | II         | +        | 72             | -                | -        | -       |
| 16      | 7        | F   | I          | -        | 58             | -                | -        | -       |
| 17      | 8        | M   | II         | +        | 72             | -                | TVR      | +       |
| 18      | 9        | M   | I          | -        | 72             | -                | -        | -       |
| 19      | 9        | M   | II         | +        | 70             | -                | -        | -       |
| 20      | 12       | F   | I          | -        | 60             | -                | -        | -       |
| 21      | 13       | M   | I          | -        | 61             | -                | -        | -       |
| 22      | 16       | F   | I          | -        | 63             | -                | -        | -       |
| 23      | 16       | F   | I          | -        | 52             | -                | -        | -       |
| 24      | 21       | F   | I          | -        | 59             | -                | -        | -       |
| 25      | 21       | M   | I          | -        | 60             | -                | -        | -       |
| 26      | 23       | M   | II         | -        | 65             | -                | -        | -       |

CTR = cardiothoracic ratio TVR = tricuspid valvular replacement  
ASD clos = closure of the atrial septal defect

wide spectrum like their clinical features and that this should be determined mainly by the function of the tricuspid valve rather than by the condition of the proximal chamber

In the patients of the Tricuspid Stenosis Dominant Type who show severe symptoms the blood flow into the distal chamber in diastole is reduced by the tricuspid stenosis, resulting in the elevation of the right atrial pressure with the right to left shunt and the decrease of the pulmonary flow. In this type of patient, the deformity is extreme and particularly as evidenced in cases No 5 and 6 the small distal chamber further reduces the output of the right ventricle

In the patients of the Tricuspid Insufficiency Dominant Type tricuspid insufficiency results in a back and forth flow of a large amount of blood between the right atrium and right ventricle and necessitates the volume overwork of both chambers resulting in severe dilatation. The mild symptoms in three patients of this type make it likely that an adequate cardiac output should be maintained despite the severe tricuspid insufficiency. The proximal chamber was relatively small compared to the dilated right atrium or the right ventricle, so it was apparent that this portion had little effect on the hemodynamics.

Dilatation of the right ventricular outflow tract which was demonstrated as the double

Table IV Right heart catheterization findings

| Case No | Pressure in mm Hg |        |      |          |               |      |   | Diastolic pressure gradient across the tricuspid valve |
|---------|-------------------|--------|------|----------|---------------|------|---|--|
|         | RA                |        |      | RV       |               |      |   |  |
|         | A wave            | V wave | Mean | Systolic | End diastolic | Mean |   |  |
| 1       | 10                | 7      | 7    | 23       | 10            | 13   | 0 |  |
| 2       | 8                 | 9      | 7    | 20       | 6             | 9    | 0 |  |
| 3       | 7                 | 8      | 5    | 20       | 4             | 7    | 3 |  |
| 4       | 6                 | 6      | 5    | 25       | 7             | 10   | 0 |  |
| 6       | 11                | 7      | 7    | 20       | 9             | 10   | 8 |  |
| 7       | 11                | 8      | 7    | 19       | 5             | 12   | 6 |  |
| 8       | 7                 | 10     | 7    | 35       | 5             | 10   | 3 |  |
| 9       | 5                 | 15     | 10   | 25       | 10            | 10   | 0 |  |
| 10      | 12                | 17     | 11   | 22       | 10            | 11   | 4 |  |
| 11      | 9                 | 11     | 9    | 24       | 8             | 12   | 0 |  |
| 13      | 8                 | 7      | 8    | 32       | 8             | 15   | 0 |  |
| 14      | 13                | 11     | 9    | 25       | 6             | 10   | 3 |  |
| 15      | 10                | 11     | 9    | 30       | 10            | 12   | 0 |  |
| 16      | 9                 | 7      | 8    | 34       | 11            | 9    | 0 |  |
| 17      | 10                | 9      | 8    | 25       | 10            | 15   | 0 |  |
| 18      | 9                 | 17     | 11   | 30       | 10            | 15   | 5 |  |
| 19      | 6                 | 9      | 5    | 22       | 9             | 10   | 0 |  |
| 20      | 7                 | 8      | 5    | 21       | 7             | 8    | 0 |  |
| 21      | 11                | 7      | 8    | 22       | 13            | 15   | 0 |  |
| 22      | 4                 | 8      | 4    | 20       | 2             | 7    | 0 |  |
| 23      | 10                | 10     | 6    | 31       | 3             | 6    | 0 |  |
| 24      | 9                 | 7      | 6    | 30       | 9             | 10   | 0 |  |
| 25      | 11                | 12     | 7    | 20       | 10            | 11   | 0 |  |
| 26      | 13                | 10     | 10   | 20       | 13            | 10   | 0 |  |

RA = right atrium RV = right ventricle

ball sign in angiocardiology was most prominent in the patients of the Tricuspid Insufficiency Dominant Type and it might be attributed to severe tricuspid insufficiency. However, the double ball sign was also observed in patients of the Tricuspid Stenosis Dominant Type who might have a mild or no tricuspid insufficiency. In addition the outflow tract in diastole was enlarged to various degrees in all patients of the Mild Type, but it was not sufficient to show the double ball sign. Based on these findings, the enlargement of the outflow tract in this anomaly should be considered to be a part of the inherent defect.

In the patients of the Mild Type it can be seen from the clinical data described previously that the function of the tricuspid valve is relatively good and that adequate pulmonary flow is maintained.

With a properly functioning tricuspid valve and

# Polymicrobial infective endocarditis An increasing clinical entity

L D Saravolatz MD  
K H Burch MD  
E L Quinn MD\*  
F Cox MD\*\*  
T Madhavan MD\*\*\*  
E Fisher MD\*\*

Detroit Mich

Among the 203 cases of infective endocarditis seen between 1903 and 1969 at the Henry Ford Hospital only one patient had polymicrobial (mixed infection) endocarditis and this case occurred after cardiac surgery. Since that time we saw nine patients with this infection. Furthermore over the last two years a polymicrobial etiology was found in 10 per cent of all of our endocarditis patients.

This experience contrasts with the 1942 report of Organ and Poston of six cases of mixed infection in bacterial endocarditis and their observation that endocarditis due to more than one organism was very uncommon. Furthermore Weinstein and Rubin found only one case of polymicrobial endocarditis in a review of 452 cases of infective endocarditis occurring from 1951 to 1966. Since then at least 21 other cases were reported by various authors with as many as four pathogens isolated in one patient.

The purpose of this paper is to describe the clinical features bacteriology and therapy of our cases review reported cases and compare endocarditis due to single and multiple organisms.

## Patients and methods

**Patients** Patients with polymicrobial endocarditis were retrospectively studied. The nine cases seen since 1969 were in heroin addicts, one of whom had recent aortic valve surgery (patient No 1, Tables I and II) while the first case encountered in 1908 occurred in a non addict after cardiac surgery (patient No 10). The criteria for the diagnosis included (1) polymicrobial bacteremia with the same organisms isolated in each of six or more blood cultures obtained over 24 hours or the isolation of two or more organisms from heart valve cultures at the time of surgery or postmortem examination (2) significant cardiac murmurs (3) fever and (4) embolization. These criteria were modified after Menda and Gorbach.<sup>4</sup>

**Treatment regimens** Antibiotic therapy was started empirically during the first two days of admission in all ten patients as clinical evidence for a diagnosis of endocarditis was present. In all cases when blood culture results were available definitive antibiotic therapy was selected on the basis of *in vitro* studies. All patients received six weeks or more of antibiotic treatment except two who died at 4 and 19 days respectively.

**Antimicrobial activity** The MIC (minimal inhibitory concentration) and MBC (minimal bactericidal concentration) of the antibiotic used for treatment of patients with bacterial endocar-

From the Division of Infectious Diseases Department of Medicine, Henry Ford Hospital, Detroit, Mich.  
This study was supported in part by grants from the Michigan Heart Association and the McGraw-Hill Foundation. A case was presented at the Third Swedish Scott's Arrhenius Infectious Diseases Conference held at St. Ingelund, Sweden, September 1966.  
Received for publication September 9, 1976.  
Accepted for publication November 30, 1976.  
Reprint requests: L. D. Saravolatz, MD, Henry Ford Hospital, 299 W. Grand Blvd., Detroit, Mich. 48202.  
Clinical Professor of Medicine, University of Michigan School of Medicine.  
Clinical Associate Professor of Medicine, University of Michigan School of Medicine.  
Clinical Associate Professor of Medicine, University of Michigan School of Medicine.

Mild Type occupy 54 per cent of the total. In cases such as this, it is difficult to decide on the suitability of operation. Genton and Blount<sup>7</sup> reported that the patients over 50 years of age had generally enjoyed good health, that cyanosis was present in only about 50 per cent, and that the cardiac silhouette on the x ray film was often nondescript but appeared to be normal or nearly so in some cases.<sup>7</sup> One of the two patients who lived till 79 years of age was asymptomatic and the other had no cardiomegaly.<sup>7</sup> These patients would be included in the Mild Type of this report. Their prognosis seems to be good, and especially some patients without any cyanosis nor symptoms may be able to live out their natural lives. However careful observation must be made of the patients with mild cyanosis because they may deteriorate at some stage in their life.

### Summary

Twenty six patients with Ebstein's anomaly were classified into three types according to their clinical features, heart catheterization data, angiocardigraphic and anatomical findings which were obtained on surgery or autopsy. The hemodynamics in each type were discussed.

**1 Tricuspid Stenosis Dominant Type** Eight patients who were cyanotic and had severe symptoms: mild to moderate cardiomegaly, and the double ball sign on angiocardigraphy were classified into this type. A pressure gradient across the tricuspid valve was demonstrated in 5 patients.

Tricuspid stenosis restricts the blood flow into the functioning right ventricle and results in the low output of the right ventricle and right to left shunt at the atrial level.

**2 Tricuspid Insufficiency Dominant Type** Four cyanotic patients who had mild symptoms despite the severe cardiomegaly were grouped into this type. The double ball sign was found

in all. In three patients incompetent tricuspid valve was observed.

Tricuspid insufficiency necessitates the volume overwork of the right atrium and the functioning right ventricle, resulting in severe dilatation.

**3 Mild Type** Fourteen patients who showed no or mild cyanosis, no or mild symptoms and mild to moderate cardiomegaly, were classified into this type.

It is considered that the adequate cardiac output in these patients is attributable to the good function of the tricuspid valve.

### REFERENCES

- 1 Ebstein W. Über einen sehr seltenen Fall von Insufficienz der Valvula Tricuspidalis bedingt durch eine angeborene hochgradige Missbildung derselben. *Arch Anat Physiol Wissensch Med* 1886 p 238.
- 2 Adams J C L and Hudson H. A case of Ebstein's anomaly surviving to age 79. *Br Heart J* 18 129 1956.
- 3 Bialostozky D, Horwitz S and Espino Verla J. Ebstein's malformation of the tricuspid valve. A review of 65 cases. *Am J Cardiol* 29 826 1972.
- 4 Elliot L P and Hartmann A F Jr. The right ventricular infundibulum in Ebstein's anomaly of the tricuspid valve. *Radiology* 90 694 1967.
- 5 Ellis K, Griffiths S P, Burris J O, Ramsay G C and Fleming R J. Ebstein's anomaly of the tricuspid valve. Angiocardigraphic considerations. *Am J Roentgenol* 92 1338 1964.
- 6 Lev M, Liberthson R R, Joseph R H, Seten C E, Kunske R D, Fekner F A O and Miller R A. The pathologic anatomy of Ebstein's disease. *Arch Pathol* 90 334 1970.
- 7 Genton E and Blount S G Jr. The spectrum of Ebstein's anomaly. *Am Heart J* 73 395 1967.
- 8 Hardy K L and Roe B B. Ebstein's anomaly. Further experience with definitive repair. *J Thorac Cardiovasc Surg* 58 553 1969.
- 9 Makous N and Vander Veer J B. Ebstein's anomaly and life expectancy. Report of a survival to over age 79. *Am J Cardiol* 18 100 1966.
- 10 Kumar A J, Fyler D C, Miettinen O S and Nadas A S. Ebstein's anomaly. Clinical profile and natural history. *Am J Cardiol* 28 84 1971.
- 11 Watson H. Natural history of Ebstein's anomaly of tricuspid valve in childhood and adolescence. An international co-operative study of 505 cases. *Br Heart J* 36 417 1974.

heroin associated cases while the heroin unrelated surgical patient developed fever nine weeks postoperatively

All were febrile on admission (38.6 to 40 °C). Shaking chills were noted by eight and pleuritic chest pain occurred in six. Septic pulmonary emboli were confirmed in two patients by multiple pulmonary infiltrates on chest x ray or lung scans that demonstrated multiple perfusion defects.

Seven of the ten had murmurs on admission and the remaining three developed a murmur within the first 24 hours after admission. In all ten the valve involved was later demonstrated by echocardiography, cardiac catheterization or postmortem examination. Echocardiograms were positive in five and cardiac catheterization was performed in six of the ten.

Splenomegaly was found in two patients and splenic infarction confirmed in another at autopsy. Two patients had multiple Roth spots while another patient had both Roth spots and *Candida chorioretinitis* on ophthalmologic examination. Another (patient No. 6) developed a septic arthritis of the left sacroiliac joint early in the course of treatment.

Two patients died. One (patient No. 8) presented in coma with hemiparesis secondary to a ruptured mycotic aneurysm of the internal carotid artery. This patient also had a brain abscess and purulent meningitis. Another (patient No. 9) developed congestive failure on the second hospital day due to acute aortic insufficiency and died.

The tricuspid and mitral valves were most commonly affected. Three patients had tricuspid insufficiency, two had mitral insufficiency, two had aortic insufficiency and one had both tricuspid and mitral insufficiency. The heroin related postsurgical patient with an aortic prosthesis developed endocarditis involving both the aortic and mitral valves. The non heroin related postsurgical patient had an atrial septal defect repair and also developed endocarditis of the mitral valve.

**Laboratory studies.** Nine patients, all heroin addicts, had leukocytosis on admission ranging from 10,800 to 48,000/mm<sup>3</sup>. Anemia was present in all patients. At admission the mean hemoglobin was 11.5 Gm/100 ml (range 10.0 to 13.8 Gm/100 ml).

The most common organism encountered was

**Table II Summary of causative organisms, serum bactericidal activity and antimicrobial therapy**

| Case no. | Organism                                | Peak SBT* | Antibiotic therapy |
|----------|---|-----------|--------------------|
| 1        | <i>S. viridans</i>                      | 1:128     | Ampicillin plus    |
|          | <i>H. influenza</i>                     | 1:4096    | Gentamicin         |
|          | <i>H. parainfluenza</i>                 | 1:256     |                    |
|          | <i>S. epidermidis</i>                   | 1:256     |                    |
| 2        | <i>S. aureus</i>                        | 1:64      | Cephalothin        |
|          | <i>Beta streptococcus</i> (group B)     | 1:128     |                    |
| 3        | <i>Corynebacterium</i>                  | 1:2       | Vancomycin plus    |
|          | <i>C. parapsilosis</i>                  | 1:7       | Amphotericin plus  |
|          |   |           | Flucytosine        |
| 4        | <i>S. aureus</i>                        | 1:128     | Methicillin plus   |
|          | <i>P. aeruginosa</i>                    | 1:8       | Tobramycin plus    |
|          |   |           | Carbenicillin      |
| 5        | <i>Beta streptococcus</i> (non group A) | 1:512     | Penicillin G plus  |
|          | <i>Streptococcus</i> (non group D)      | 1:512     | Gentamicin         |
| 6        | <i>P. aeruginosa</i>                    | 1:16      | Carbenicillin plus |
|          | <i>S. faecalis</i>                      | 1:128     | Tobramycin plus    |
|          |   |           | Ampicillin         |
| 7        | <i>S. aureus</i>                        | 1:512     | Cefazolin plus     |
|          | <i>P. aeruginosa</i>                    | 1:16      | Carbenicillin plus |
|          |   |           | Gentamicin         |
| 8        | <i>S. faecalis</i>                      | 1:8       | Ampicillin plus    |
|          | <i>P. aeruginosa</i>                    | ND†       | Streptomycin       |
| 9        | <i>S. faecalis</i>                      | ND†       | Methicillin        |
|          | <i>P. aeruginosa</i>                    | ND†       |                    |
| 10       | <i>S. epidermidis</i>                   | ND†       | Penicillin plus    |
|          | <i>S. viridans</i>                      | ND†       | Streptomycin       |

Serum bactericidal titer ag not specific organisms isolated  
†Not done

*P. aeruginosa* in five patients followed by *S. faecalis* and *S. aureus* in three. *Candida parapsilosis*, *Corynebacteria*, *H. influenza*, *H. parainfluenza*, *S. epidermidis* and four different strains of streptococci were the other organisms isolated. The most common combinations of organisms were *S. faecalis* and *P. aeruginosa* in three cases and *S. aureus* and *P. aeruginosa* in two.

**Treatment and outcome.** Multiple antibiotics were usually employed (8 of 10 cases) as illustrated in Table II. On the other hand, antibiotic therapy with cephalothin alone was given in one case (patient No. 2) since both organisms were susceptible to this antibiotic. In the only other case (patient No. 9) treated with a single antibiotic, the second organism was not isolated from the initial culture until after the patient had died.

Of the eight patients given antibiotic therapy



**Table 1** Clinical features of ten patients with polymicrobial endocarditis treated at the Henry Ford Hospital

| Case no | Age & sex | Race | Addic tion | Post surgery | Valve         | Organism   | Surgical treatment                     | Outcome   |
|---------|-----------|------|------------|--------------|---------------|--|--|---|
| 1       | 25 M      | B    | +          | +            | Aortic Mitral | <i>S. viridans</i><br><i>H. influenza</i><br><i>H. parainfluenza</i><br><i>S. epidermidis</i><br><i>S. aureus</i>  | None                                   | Cured   |
| 2       | 24 F      | B    | +          | -            | Mitral        | <i>B. streptococcus</i> (group B)<br><i>Corynebacterium</i><br><i>C. parapsilosis</i><br><i>S. aureus</i><br><i>P. aeruginosa</i>  | None                                   | Cured   |
| 3       | 39 M      | B    | +          | -            | Aortic        | <i>Corynebacterium</i><br><i>C. parapsilosis</i><br><i>S. aureus</i><br><i>P. aeruginosa</i>   | Aortic valve replacement               | Cured   |
| 4       | 25 M      | B    | +          | -            | Tricuspid     | <i>S. aureus</i><br><i>P. aeruginosa</i>   | None                                   | Relapsed with <i>P. aeruginosa</i> . Subsequently cured with gentamicin, carbenicillin and probenecid |
| 5       | 24 M      | B    | +          | -            | Tricuspid     | <i>B. streptococcus</i> (non group A)<br>Non hemolytic <i>streptococcus</i> (non group D)  | None                                   | Cured   |
| 6       | 24 M      | B    | +          | -            | Mitral        | <i>P. aeruginosa</i>   | None                                   | Cured   |
| 7       | 26 M      | B    | +          | -            | Tricuspid     | <i>S. faecalis</i><br><i>S. aureus</i><br><i>P. aeruginosa</i><br><i>P. aeruginosa</i><br><i>S. faecalis</i><br><i>P. aeruginosa</i><br><i>S. faecalis</i><br><i>P. aeruginosa</i> | Tricuspid valvectomy                   | Cured   |
| 8       | 37 M      | B    | +          | -            | Mitral        | <i>S. faecalis</i><br><i>P. aeruginosa</i><br><i>S. faecalis</i><br><i>P. aeruginosa</i>   | None                                   | Died on 19th hospital day   |
| 9       | 25 M      | B    | +          | -            | Aortic        | <i>S. faecalis</i><br><i>P. aeruginosa</i>   | Scheduled for aortic valve replacement | Died on 4th hospital day  |
| 10      | 30 M      | W    | -          | +            | ASD Mitral    | <i>S. albus</i><br><i>S. viridans</i>  | None                                   | Relapsed with <i>S. epidermidis</i> alone. Subsequently cured with Penicillin and Streptomycin        |

ditis were determined by the twofold dilution technique using trypticase soy broth (BBL). The inoculum consisted of approximately  $10^8$  organisms. The MIC was defined as the lowest concentration of antibiotic that inhibited visible growth of bacteria after incubation for 18 hours at 37°C. The MBC of each isolate was defined as the highest dilution from which no more than 20 colonies grew after 0.01 ml loopful was subcultured on 10 per cent sheep blood agar and incubated overnight. When vancomycin was used the end point was 50 rather than 20 persisting colonies.

Bactericidal titers of serum were determined by the twofold dilution technique with trypticase soy broth as the diluent using a similar inoculum and end point as described above.

## Results

**Clinical features** The salient features of our ten patients are summarized in Table 1. The age ranged between 24 and 39 years with a mean age of 27.9 years. There were nine males and one female. The female patient was diagnosed and treated during the second trimester of pregnancy. Nine were heroin addicts, some for as long as 11 years. While eight had no previous history of cardiac disease, two had previous cardiac surgery. One patient had undergone a repair of an atrial septal defect nine weeks earlier, and one of the heroin-related cases had an aortic valve replacement three months prior to developing polymicrobial endocarditis. The average duration of symptoms was 16 days prior to seeking medical attention, with a range of 3 to 35 days in the

instances clinical features were present that suggested a second organism. One (patient No. 6) addict while being treated for enterococcal endocarditis developed septic arthritis of the sacroiliac joint. Monoarticular septic arthritis and adjacent flat bone osteomyelitis have been described in heroin addicts and are usually due to *S. aureus* and *P. aeruginosa*. The latter organism was subsequently recovered from initial blood cultures. With less virulent organisms such as viridans streptococci or enterococci migratory polyarthritis has been described but septic arthritis is rare.

In another patient (patient No. 3) the presence of *Candida* chorioretinitis and Roth spots suggested a polymicrobial etiology. Roth spots may be associated with either bacterial or fungal endocarditis but chorioretinitis or endophthalmitis is suggestive of a fungal etiology. In this patient blood cultures revealed corynebacterium after 48 hours of incubation while *C. parapsilosis* was identified after 5 days.

In the last instance (patient No. 6) when blood cultures initially grew only *S. faecalis* septic pulmonary emboli suggested an additional etiologic agent. Septic pulmonary emboli occur in endocarditis due to more virulent organisms infecting the tricuspid valve. With organisms such as viridans streptococci or enterococci emboli do not occur possibly because these organisms do not usually infect right sided valves. In this patient after 96 hours of incubation the initial blood cultures also grew *P. aeruginosa*.

Antimicrobial therapy we employed usually was with a combination of agents appropriate for each organism. Although increased adverse reactions may have been expected they were not encountered possibly because we did not routinely utilize high dose ( $> 11$  mg/Kg/day) aminoglycoside therapy in the treatment of gram negative bacillary endocarditis.

In our series as well as in previous reports of endocarditis due to a single agent gram positive organisms were eradicated when peak bactericidal titers 8 to 32 times the minimal inhibitory concentrations were achieved.

As reported by others eradication of gram negative bacilli causing endocarditis did not relate to peak serum bactericidal titers. This in part may relate to falsely elevated in vitro titers which can result from alkalization of serum which occurs on standing. Recent reports showed that the use of aminoglycoside antibiotics

at dosages generally considered toxic were associated with a higher percentage of medical cures in endocarditis due to gram negative bacilli. One in our series (patient No. 4) who relapsed was cured when retreated with carbencillin, probenecid and an aminoglycoside at doses of 150 per cent those originally utilized.

Surgery plays a significant role in the treatment of patients with polymicrobial endocarditis. While 15 per cent of patients with single organism endocarditis may need surgery, 52 per cent of patients with polymicrobial endocarditis required surgery. The high incidence of surgery may relate to the frequent occurrence of *Candida* (23 per cent) and *P. aeruginosa* (29 per cent) as causative agents. Fungal endocarditis is seldom cured medically and surgical extirpation of the infected valve may be required. In *Pseudomonas* endocarditis medical failure has been common and surgical removal of the valves has been used for intractable infection. Finally *S. aureus* present in more than 50 per cent of the endocarditis patients in this series is frequently associated with residual valvular disorders such as aortic insufficiency which may require surgery for intractable failure.

This study and recent reports therefore indicate that polymicrobial endocarditis occurs mainly in patients abusing heroin and/or having recently undergone cardiac surgery. To decrease mortality rate and morbidity early aggressive antibiotic therapy may be indicated even in a suspected case of polymicrobial endocarditis. Specific therapy should be selected on the basis of in vitro studies for each causative organism. The ultimate outcome of a patient with polymicrobial endocarditis was related to the type of infecting pathogen rather than to the number of pathogens present. Treatment usually required use of two or more antibiotics and adverse effects may be encountered since toxic doses of aminoglycosides may be necessary to eradicate gram negative bacilli. When a fungus is one of the organisms cultured or if hemodynamically significant abnormalities occur early surgery should be considered as patients with polymicrobial endocarditis are usually young and otherwise healthy.

### Summary

Polymicrobial endocarditis was very uncommon until ten years ago. However since that time at least 21 cases were reported and 10 patients with this mixed infection were seen at

Table III Summary of treatment and outcome of 31 cases of polymicrobial endocarditis

| Reference                      | No of cases | Treatment |                    | Heroin related | Postcardiotomy | Died |
|--------------------------------|-------------|-----------|--------------------|----------------|----------------|------|
|                                |             | Medical   | Medical & surgical |                |                |      |
| (1969 71) Reyes et al *        | 1           | 1         | 3                  |                |                |      |
| (1971 72) Harris et al *       | 4           | 0         | 4                  | 4              | 0              | 1    |
| (1967 71) Banks et al          | 3           | 1         | 2                  | 4              | 0              | 1    |
| (1971) Menda & Gorbach         | 1           | 1         | 0                  | 3              | 0              | 2    |
|                                |             |           |                    | 1              | 0              | 0    |
| (1969 71) Dreyer & Fields      | 1           | NG        | NG                 | 1              | 0              | 0    |
| (1967) Childs et al *          | 1           | 1         | 0                  |                |                |      |
| (1968 69) Hermans & Washington | 3           | NG *      | NG *               | 1              | 0              | 0    |
|                                |             |           |                    | 0              | 3              | *    |
| (1971) Simberloff et al        | 1           | 0         | 1                  | 1              | 0              | 0    |
| (1969 74) Mills & Drzew *      | 3           | 2         | 1                  | 2              | 0              | 2    |
| (1958 75) Current series       | 10          | 7         | 3                  | 9              | 2              | 2    |
| Total                          | 31          | 13/27     | 14/27              | 26             | 5              | 10   |
| Per cent                       |             | 48        | 52                 | 84             | 16             | 32   |

Not given

alone, six were cured, although two required a second course of antibiotics. The two treatment failures in this group were due to inappropriate antibiotics (patient No 8) and acute aortic insufficiency (patient No 9).

Of the two patients given antibiotic therapy combined with surgical excision of the infected valve (patients No 3 and 7) both were cured. One, with *Candida* endocarditis was aggressively managed after several days of antibiotic therapy based on presently recognized methods of managing such infections. The other patient had *Pseudomonas tricuspid* endocarditis and was treated surgically after relapse following antibiotic therapy.

**Summary of review of reported cases.** As previously noted polymicrobial endocarditis was an uncommon occurrence prior to 1966. At least 21 cases of polymicrobial endocarditis were reported since 1966 (Table III). Seventeen of these (81 per cent) were related to heroin use (three (14 per cent) occurred after cardiac surgery and one patient had rheumatic heart disease. In these cases, the most commonly encountered organisms were *S. aureus* (14), *Candida* (six), non-group D streptococci (five), *P. aeruginosa* (four) and *Serratia* (three).

When the 21 cases previously reported are combined with our ten cases (Table III) only 48 per cent were treated with medical therapy alone. In addition 52 per cent needed cardiac surgery

either for treatment of intractable infection or repair of hemodynamically significant problems related to the infection. Finally, even with aggressive combined medical and surgical therapy, the mortality rate was 32 per cent.

### Discussion

Recently mixed or polymicrobial bacteremias have become frequent. In 1970 Hermans and Washington reported a 6 per cent incidence among all patients with bacteriologically established bacteremia. Patients identified as being at high risk for mixed infections were premature infants and patients with hematologic malignancies or gastrointestinal diseases. Recognition of polymicrobial bacteremia is important, because it is associated with high mortality rate (37 to 81 per cent).<sup>7</sup> Furthermore these investigators reported only three patients with the rare entity of polymicrobial endocarditis or endarteritis among the 46 cases of polymicrobial bacteremia. All three cases followed cardiac surgery. Only two of our ten cases had undergone previous cardiac surgery. On the other hand the patient profile in the other eight patients with mixed endocarditis was quite different. They were young heroin addicts with no prior underlying cardiovascular disease.

In our cases polymicrobial endocarditis was usually indistinguishable from endocarditis caused by a single organism. However in three

# Abrupt propranolol withdrawal in angina pectoris Effects on platelet aggregation and exercise tolerance\*

William H. Frishman M.D.  
James Christodoulou M.D.  
Babette Weksler M.D.  
Charles Smithen M.D.  
Thomas Kilip M.D.  
Stephen Scheidt M.D.  
New York N.Y.

Propranolol has been shown conclusively to be a relatively safe and efficacious drug for the treatment of most patients with angina pectoris. In dosage sufficient to improve exercise tolerance, it has also been demonstrated to restore towards normal the increased platelet aggregability noted in patients with angina pectoris. However, it has recently been suggested that abrupt discontinuation of propranolol after long term therapy may have adverse effects, precipitating myocardial infarction and sudden death. To further evaluate the possible mechanisms for the occasional adverse clinical effects of propranolol withdrawal, data are presented from a study designed to measure exercise tolerance and platelet aggregation in patients with angina pectoris before during and after propranolol treatment. The protocol for study was devised and carried out before reports appeared suggesting possible adverse effects from abrupt withdrawal of the drug. Because of these reports, the accumulated data were analyzed for possible rebound effects

and the results form the subject of the present study.

## Methods

**Patients** The study population consisted of 20 patients, 14 men and 6 women, aged 35 to 69 (mean 54) years of age. Criteria for inclusion were (1) at least three attacks of angina pectoris per week with no evidence of an accelerated course (unstable angina) in the 6 months prior to study; (2) absence of valvular heart disease, hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes, hypoprotein abnormalities, anemia, smoking history, or myocardial infarction within 6 months of study; and (3) angiographic narrowing of at least 70 per cent of one or more of the coronary arteries and definite electrocardiographic (ECG) evidence of myocardial ischemia associated with chest pain during submaximal exercise stress testing.

Ten age and sex matched normal subjects with a negative exercise stress test were also studied. These normal subjects had no evidence of ischemic vascular disease, lipid abnormalities, or diabetes, and each had a negative history for cigarette smoking and drug ingestion of any sort.

**Experimental design** All normal subjects had platelet aggregation studies and exercise tests as described below.

The patients with angina pectoris were seen biweekly by the same physician. Informed consent was obtained and all cardiovascular medications were discontinued with the exception

From the Divisions of Cardiology and Hematology, Department of Medicine, The New York Hospital-Cornell Medical Center, New York, N.Y.

This work was supported by contract USPHS 43-67-1439 by a grant from the New York Heart Association and a grant from the Albany Laboratory, New York, N.Y.

Received for publication Sept. 13, 1976

Accepted for publication Nov. 18, 1976

Reprint requests: Dr. William Frishman, Hospital of the Albert Einstein College of Medicine, 1255 Eastchester Road, Bronx, N.Y. 10461.

Presented in part at the 44th Scientific Session of the American Heart Association, Anaheim, California, November 18th, 1975.

our hospital. All, except one of these infections, occurred in patients who had undergone heart surgery or abused intravenous drugs. Although generally clinically indistinguishable from mono-microbial endocarditis, these mixed infections carried a very high mortality rate (> 30 per cent) and an unusually large number of the patients (> 50 per cent) needed heart surgery either to control the infection or to repair cardiac defects resulting from the infection. The prognosis depended on the species rather than the number of organisms isolated and on aggressive antimicrobial and surgical therapy.

We wish to thank D. Pohlod, M.S., and M. Somerville for technical support and S. Barry, M.N., for clinical assistance.

#### REFERENCES

- Orgain E S and Poston M A. Mixed infections in bacterial endocarditis. *Am Heart J* 23:823 1942.
- Weinstein L and Rubin R H. Infective endocarditis—1973. *Progr Cardiovasc Dis* 16:239 1973.
- Banks T, Fletcher R and Ah N. Infective endocarditis in heroin addicts. *Am J Med* 55:444 1973.
- Reyes M P, Palutke W A, Wylin R F and Lerner A M. *Pseudomonas* endocarditis in the Detroit Medical Center 1969-1972. *Medicine* 52:173 1973.
- Harris D D, Yeoh C B, Breault J et al. Fungal endocarditis secondary to drug addiction. *J Thorac Cardiovasc Surg* 43:980 1972.
- Child J A, Darrell J H, Davies N R et al. Mixed infective endocarditis in a heroin addict. *J Med Microbiol* 2:293 1969.
- Hermans J E and Washington J A II. Polymicrobial bacteremia. *Ann Intern Med* 73:387 1970.
- Menda K M and Gorbach S L. Favorable experience with bacterial endocarditis in heroin addicts. *Ann Intern Med* 78:25 1973.
- Dreyer N P and Fields B N. Heroin associated infective endocarditis. *Ann Intern Med* 78:699 1973.
- Simberloff M S et al. Two stage tricuspid valve replacement for mixed bacterial endocarditis. *Arch Intern Med* 133:212 1974.
- Mills J and Drew D. Serratia Marcescens endocarditis: A regional illness associated with intravenous drug abuse. *Ann Intern Med* 84:29 1976.
- Lutkin E G et al. Mixed septicemia and gastrointestinal disease. *Am J Dig Dis* 11:930 1966.
- Salihuddin N I, Madhavan T, Fisher E J, Cox F, Quinn E L and Evler W R. *Pseudomonas osteomyelitis*. *Radiology* 109:41 1973.
- Chase R M. Infective endocarditis today. *Med Clin North Am* 57:1383 1973.
- Mandell G L, Kaye D, Levinson M E and Hook E W. Enterococcal endocarditis. *Arch Intern Med* 125:258 1970.
- Geraci J E. The antibiotic therapy of bacterial endocarditis. *Med Clin North Am* 42:1101 1958.
- Quinn E L and Cox F. Bacterial endocarditis based on experience with 203 patients. In: Hagan B M. *Antimicrobial therapy*. Philadelphia 1970. W B Saunders Company.
- Finland M. Current status of therapy in bacterial endocarditis. *JAMA* 166:364 1958.
- Bryan C S et al. Gram negative bacillary endocarditis. *Am J Med* 58:209 1975.
- Reyes M P et al. *Pseudomonas* endocarditis: Improved rate of medical cure 1971-1974 (Abstr). Program 15th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 1975. No 184.
- Quinn E L, Madhavan T, Salihuddin N, Cox F and Fisher E. The increasing role of surgical therapy in bacterial endocarditis. *Surg Clin North Am* 52:1461 1972.
- Kaye D. Infective endocarditis. Baltimore 1976. University Park Press p 124.
- Arbush A, Thomas N W, Chiscano A and Wilson H F. Total tricuspid valvectomy without replacement in the treatment of *Pseudomonas* endocarditis. *Surg Forum* 22:162 1971.

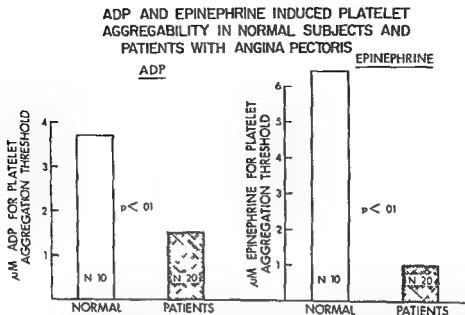


Fig 2 Comparison of ADP and epinephrine induced platelet aggregability in normal subjects and patients with angina pectoris. Platelets of normal subjects require significantly higher concentrations of ADP (left panel) and epinephrine (right panel) to attain aggregation threshold than do platelets of patients with angina pectoris

analysis. The specimens were coded so that those performing the aggregation studies had no knowledge of the patient's diagnosis or type of drug therapy.

Platelet aggregation studies were performed using the turbidometric method of Born as modified by Mustard and colleagues<sup>3</sup> and previously reported from this laboratory.<sup>8</sup> The aggregating agents used were ADP and epinephrine. The ADP concentrations producing irreversible aggregation in untreated patients and normal subjects were 0.5, 1, 2, 5, 10, 20, and 100  $\mu\text{M}$ . Comparable epinephrine concentrations for aggregation were in the range of 0.05 to 5500  $\mu\text{M}$ . The lowest concentration producing a full biphasic response was recorded as the threshold dose. The threshold concentration of ADP and epinephrine was assessed without extrapolation between different concentrations. The change in light transmittance to increasing concentrations of ADP and the characteristic biphasic response at the threshold are illustrated in Fig 1. In repeated ADP and epinephrine determinations using coded samples, reproducibility was within 10 per cent of mean.

**Exercise testing.** Bicycle ergometry testing was performed by another examiner who had no knowledge of the subject's drug status during the study. A modification of the ear ensiform system

of Arbarquez and associates<sup>14</sup> was used with three apical leads recorded in the supine position and on the bicycle ergometer prior to exercise.

Multistage graded exercise was performed utilizing a bicycle ergometer (Schwinn ergometric exerciser) as the patient pedaled against a predetermined load. After blood for platelet studies had been obtained, patients were started at a work load of 150 kpm/minute which was increased in increments of 150 kpm every three minutes until chest pain, fatigue, or a heart rate of 160 per minute occurred. An abnormal electrocardiographic response was defined as a flat or down sloping ST segment depression of at least 1 mm persisting for at least 0.08 sec after the termination of the QRS complex with the P-Ta segment as the baseline of reference.

Blood pressure in the brachial artery was recorded by sphygmomanometer prior to and immediately after exercise. The heart rate blood pressure product, an indirect assessment of myocardial oxygen consumption,<sup>15</sup> was calculated from measurements obtained immediately after cessation of exercise.

The incidence of other ECG changes (bundle branch block patterns, ventricular premature contractions) was also noted.

**Propranolol blood levels.** Assay of the level of propranolol in blood was performed on coded

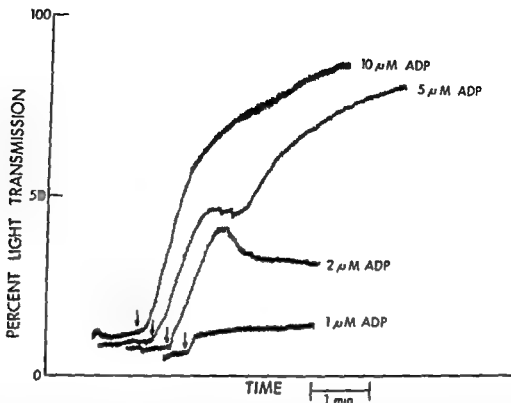


Fig 1 Aggregation response of platelets from a normal subject induced by increasing concentrations of adenosine diphosphate (ADP). Degree of aggregation is related to the increase in light transmission since clumping reduces light absorption. ADP is added to stirred platelet rich plasma at the arrows. 5  $\mu$ M ADP induces the characteristic biphasic aggregation threshold response of an initial plateau followed by maximal aggregation. 1  $\mu$ M and 2  $\mu$ M ADP are inadequate to achieve threshold of maximal aggregation. 10  $\mu$ M ADP induces maximal aggregation but at this higher concentration the biphasic threshold cannot be detected. (From Frishman W, Weksler B, Christodoulou J, et al. Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. *Circulation* 50:887, 1974. Reproduced by permission of the American Heart Association, Inc.)

of nitroglycerin. An oral placebo\* was administered for 11 weeks. Every patient had a resting electrocardiogram, chest roentgenogram, urinalysis, and blood analysis for cholesterol, triglycerides, glucose, blood urea nitrogen, creatinine, phosphokinase (CPK), lactic dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), hematocrit, hemoglobin, white blood cell count, and platelet count. Platelet aggregation studies were performed and exercise testing on a bicycle ergometer was carried out as described below. After the 6 week placebo period, subjects with angina pectoris were randomized into placebo ( $n = 10$ ) and propranolol ( $n = 10$ ) treatment groups. The placebo group remained on the same placebo regimen while the drug treatment group was started on 160 mg daily of oral propranolol in 4 divided doses. Neither the patient nor the physician knew whether the therapy was placebo or drug. All patients

continued taking nitroglycerin as needed. After 16 and again after 50 weeks of therapy, serum propranolol levels were determined and platelet aggregation studies and exercise tolerance tests were repeated. At this time, both placebo and propranolol therapy was abruptly stopped. In the propranolol treated group, five patients were withdrawn and given placebo and five received no further medications whatsoever. Final propranolol blood levels, platelet aggregation studies, and exercise tolerance tests were repeated 48 hours after cessation of the study medications.

**Platelet aggregation studies.** Blood was obtained after a twelve hour fast. Following an initial resting period of 30 minutes, a 19 gauge needle was inserted without use of a tourniquet into an antecubital vein and a slow infusion of physiological saline begun. After 15 minutes of rest with the patient relaxed, blood was sampled by free flow into plastic tubes containing 1/10 volume acid citrate dextrose (ACD). The blood specimens were then immediately processed for

\*Mannitol 250 mg (Ayerst Laboratories)

Table IB Individual and group mean (geometric mean) concentrations of ADP and epinephrine induced platelet aggregation in patients with angina pectoris treated with propranolol and placebo and following abrupt treatment withdrawal\*

| Angina<br>plus<br>treat d | Age | Control        |               | Placebo<br>(18 weeks) |               | Placebo<br>(50 weeks) |               | Withdrawal     |               |
|---------------------------|-----|----------------|---------------|-----------------------|---------------|-----------------------|---------------|----------------|---------------|
|                           |     | ADP ( $\mu$ M) | Ep ( $\mu$ M) | ADP ( $\mu$ M)        | Ep ( $\mu$ M) | ADP ( $\mu$ M)        | Ep ( $\mu$ M) | ADP ( $\mu$ M) | Ep ( $\mu$ M) |
| 1                         | 54  | 2              | 5.5           | 2                     | 5.5           | 1                     | 5.5           | 1              | 5.5           |
| 2                         | 60  | 2              | 5.5           | 2                     | 5.5           | 2                     | 5.5           | 2              | 5.5           |
| 3                         | 48  | 2              | 5.5           | 2                     | 5.5           | 5                     | 5.5           | 5              | 5.5           |
| 4                         | 38  | 5              | 5.5           | 2                     | 5.5           | 5                     | 5.5           | 5              | 5.5           |
| 5                         | 54  | 2              | 5.5           | 5                     | 5.5           | 1                     | 5.5           | 1              | 27.5          |
| 6                         | 55  | 2              | 5.5           | 1                     | 5.5           | 2                     | 5.5           | 5.5            | 5.5           |
| 7                         | 40  | 2              | 5.5           | 2                     | 5.5           | 2                     | 5.5           | 2              | 5.5           |
| 8                         | 59  | 2              | 5.5           | 2                     | 5.5           | 1                     | 5.5           | 2              | 5.5           |
| 9                         | 57  | 1              | 5.5           | 1                     | 5.5           | 2                     | 5.5           | 1              | 5.5           |
| 10                        | 53  | 5.5            | 5.5           | 1                     | 5.5           | 5.5                   | 5.5           | 2              | 5.5           |
|                           |     | 1.8            | 1.4           | 1.78                  | 1.4           | 1.55                  | 1.4           | 1.55           | 1.32          |

| Angina—<br>propranolol<br>treated | Age | Control        |               | Propranolol<br>160 mg per day<br>(16 weeks) |               | Propranolol<br>160 mg per day<br>(50 weeks) |               | Withdrawal     |               |
|-----------------------------------|-----|----------------|---------------|---|---------------|---|---------------|----------------|---------------|
|                                   |     | ADP ( $\mu$ M) | Ep ( $\mu$ M) | ADP ( $\mu$ M)                              | Ep ( $\mu$ M) | ADP ( $\mu$ M)                              | Ep ( $\mu$ M) | ADP ( $\mu$ M) | Ep ( $\mu$ M) |
| 1                                 | 5   | 5              | 5.5           | 5   | 5.5           | 5   | 27.5          | 5              | 5.5           |
| 2                                 | 60  | 2              | 5.5           | 5   | 5.5           | 5   | 5.5           | 5              | 5.5           |
| 3                                 | 34  | 2              | 5.5           | 2   | 5.5           | 5   | 5.5           | 1              | 5.5           |
| 4                                 | 48  | 2              | 5.5           | 5   | 5.5           | 2   | 5.5           | 1              | 5.5           |
| 5                                 | 54  | 2              | 5.5           | 2   | 5.5           | 5   | 27.5          | 2              | 5.5           |
| 6                                 | 57  | 2              | 5.5           | 2   | 5.5           | 5   | 27.5          | 2              | 5.5           |
| 7                                 | 48  | 2              | 5.5           | 2   | 5.5           | 10  | 27.5          | 2              | 5.5           |
| 8                                 | 50  | 2              | 5.5           | 5   | 27.5          | 5   | 5.5           | 1              | 5.5           |
| 9                                 | 59  | 1              | 5.5           | 5   | 5.5           | 5   | 5.5           | 1              | 5.5           |
| 10                                | 53  | 1              | 5.5           | 2   | 5.5           | 5   | 27.5          | 5              | 5.5           |
|                                   |     | 1.37           | 1.07          | 3.43†                                       | 12.9†         | 4.9‡  | 13.2‡         | 1.0‡           | 0.57‡         |

\*See Table IA for baseline and other footnotes

angina pectoris. In the 10 patients who received propranolol (160 mg/d) total work increased by 130 per cent from a control of  $765 \pm 125$  kpm to  $1790 \pm 285$  kpm after propranolol ( $p < 0.01$ ). This beneficial effect on work performance was associated with a significant drop in the heart rate blood pressure product from  $16800 \pm 1540$  to  $12000 \pm 885$  after propranolol ( $p < 0.01$ ). In 10 patients on propranolol typical anginal pain still was the end point.

Forty eight hours after abrupt propranolol withdrawal all patients returned to their pretreatment exercise tolerance level. In some instances performance was less than the control state. After 50 weeks of propranolol therapy just prior to drug withdrawal mean work level was  $1690 \pm 200$  kpm but fell 63 per cent to  $630 \pm 170$  kpm ( $p < 0.1$ ) 48 hours after propra-

nolol cessation (Fig 7 Table II). The product of heart rate and blood pressure ( $HR \times BP$ ) was  $11200 \pm 1300$  after 50 weeks of propranolol therapy and increased to  $15500 \pm 513$  following drug withdrawal ( $p < 0.1$ ) (Fig 8 Table II). The decline in work performance was similar whether propranolol treated patients were withdrawn onto placebo or off all treatment. There were no significant differences in work performance or  $HR \times BP$  in placebo treated patients when values obtained during the control period during placebo therapy and after withdrawal of placebo were compared.

All patients withdrawn from propranolol noted increased frequency of anginal pains however no myocardial infarctions or arrhythmias occurred. Propranolol therapy was quickly reinstituted in all patients following completion of studies. No



**Table 1A** Individual and group mean\* concentrations of ADP and epinephrine induced platelet aggregation in normal subjects

| Normal subjects | Age | ADP ( $\mu\text{M}^*$ ) | Epi ( $\mu\text{M}^*$ ) |
|-----------------|-----|-------------------------|-------------------------|
| 1               | 47  | 2                       | 5.5                     |
| 2               | 46  | 5                       | 5.5                     |
| 3               | 55  | 5                       | 5.5                     |
| 4               | 45  | 2                       | 27.5                    |
| 5               | 56  | 5                       | 27.5                    |
| 6               | 54  | 5                       | 27.5                    |
| 7               | 52  | 10                      | 5.5                     |
| 8               | 48  | 5                       | 0.5                     |
| 9               | 60  | 1                       | 5.5                     |
| 10              | 55  | 5                       | 5.5                     |
|                 |     | 3.72                    | 6.46                    |

Abbreviations ADP = adenosine diphosphate Epi = epinephrine  
Geometric mean

\*Values different from control value at  $p < 0.01$  confidence level

†No significant difference compared to values at 18 weeks.

‡Values different from 50 weeks at  $p < 0.01$  confidence level no difference compared to control value.

samples obtained at least 2 hours after the last tablet of propranolol or placebo was ingested and just prior to exercise testing. The serum levels were measured in double blind fashion, using the fluorometric methods of Black and colleagues<sup>16</sup> as modified by Coltart and Shand.<sup>17</sup>

**Statistical analysis** For all of the variables except platelet aggregation data arithmetic means with the standard error of the mean are presented and Student's *t* test for paired and unpaired data were employed. For aggregation data geometric means are presented. Geometric means are preferred since the concentrations of ADP and epinephrine used were essentially geometric dilutions. The Wilcoxon Rank Sum Test was used for tests of significance comparing platelet aggregability of normal subjects, untreated angina patients and treated angina patients. Comparison of aggregation data from the same patient group treated with various experimental protocols were done with the Wilcoxon Signed Rank Test and the Sign Test.

## Results

**Platelet aggregation studies** Before propranolol therapy, patients with angina pectoris demonstrated increased platelet sensitivity to aggregating concentrations of both ADP and epinephrine when compared with normal subjects. The mean concentration of ADP necessary

for the biphasic threshold response and maximal aggregation was  $1.55 \mu\text{M}$  in patients and  $3.72 \mu\text{M}$  in normal subjects, ( $p < 0.01$ ). Mean epinephrine concentration for maximal aggregation was  $1.26 \mu\text{M}$  in patients and  $6.46 \mu\text{M}$  in normal subjects ( $p < 0.01$ ) (Fig 2 Table I).

Serial studies performed on the patients receiving placebo showed no change in the increased platelet sensitivity to either ADP or epinephrine. Following abrupt placebo withdrawal, no change in platelet aggregation threshold was observed (Figs 3 and 4, Table I).

Administration of propranolol in a dose of 160 mg per day had a dramatic effect in reducing platelet sensitivity to ADP and epinephrine in patients with angina pectoris. After 16 weeks of propranolol therapy a mean of  $3.43 \mu\text{M}$  ADP was required to produce a biphasic aggregation response compared to  $1.32 \mu\text{M}$  before therapy ( $p < 0.01$ ). With epinephrine,  $12.9 \mu\text{M}$  was required after propranolol therapy in contrast to  $1.02 \mu\text{M}$  before therapy ( $p < 0.01$ ). No additional changes were noted in ADP or epinephrine platelet aggregation threshold after 50 weeks of propranolol therapy.

Following abrupt propranolol withdrawal, harvested platelets demonstrated marked increase in sensitivity to aggregating agents. Only  $1.0 \mu\text{M}$  ADP was now required to aggregate platelets and only  $0.57 \mu\text{M}$  epinephrine threshold values significantly lower than the aggregating concentrations required during propranolol therapy (Figs 5 and 6 Table I). In six of 10 patients the platelets were even more hyperaggregable than in the control state before initiation of propranolol therapy.

Mean serum concentration of propranolol was  $47 \pm 9 \text{ ng/ml}$  (range 25 to  $120 \text{ ng/ml}$ ) at a dose level of 160 mg per day and  $1 \pm 8 \text{ ng/ml}$  48 hours after treatment withdrawal.

There were no significant changes from control in the mean levels of blood glucose, urea nitrogen, serum glutamic oxaloacetic transaminase, creatine phosphokinase, lactic dehydrogenase, cholesterol, triglycerides, hematocrit or platelet count during the serial sampling periods or after abrupt propranolol withdrawal.

**Exercise tests** During the control period all 20 patients with angina pectoris had a positive electrocardiographic response to exercise. Administration of propranolol was followed by significant increase in exercise tolerance in the patients with

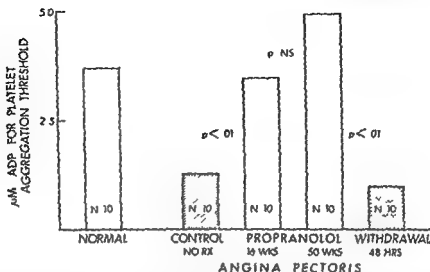
EFFECTS OF ORAL PROPRANOLOL THERAPY  
AND SUDDEN PROPRANOLOL WITHDRAWAL  
ON ADP INDUCED PLATELET AGGREGABILITY

Fig 5 Effect of propranolol and its sudden withdrawal on ADP induced platelet aggregability in patients with angina pectoris. After propranolol, platelets of treated patients are less sensitive to ADP (geometric mean) compared to before treatment and not significantly different from normal. Forty-eight hours following abrupt propranolol withdrawal platelets of patients have returned to their pretreatment hyper responsiveness to ADP.

the heart rate blood pressure product ( $HR \times BP$ ) at the end point of exercise. Forty eight hours following propranolol withdrawal exercise tolerance was significantly reduced and  $HR \times BP$  increased. Similar effects occurred whether the patients were withdrawn to placebo or to no treatment. As has been shown by others,<sup>9</sup> the changes in  $HR \times BP$  presumably paralleled changes in myocardial oxygen demand. Forty eight hours was chosen as the point of restudy following propranolol withdrawal since pharmacological studies have shown that most known cardiovascular effects of the drug are no longer present by that time.<sup>8</sup>

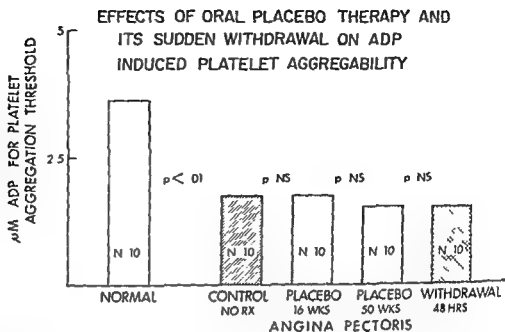
This study was performed before the appearance of several case reports citing episodes of myocardial infarction and sudden death following abrupt propranolol withdrawal.<sup>1</sup> Subsequently other investigators have noted the same phenomenon in larger series with problems generally occurring within two weeks of propranolol cessation.<sup>10</sup>

In this study, no cases of myocardial infarction or threatening arrhythmias were observed in patients withdrawn from propranolol but every patient did note a subjective increase in anginal

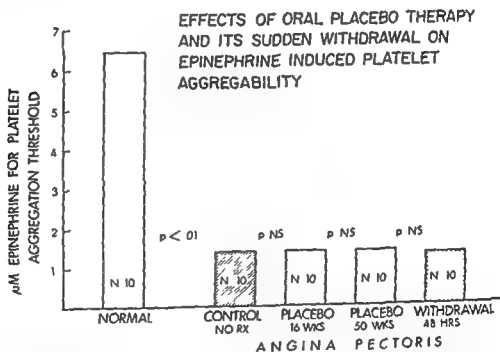
symptoms. In each subject therapy was quickly reinstituted following the two day withdrawal study. In contrast to the findings seen with propranolol withdrawal, no deterioration in exercise performance was noted following withdrawal of chronic placebo therapy, nor was there significant change in subjective anginal symptomatology.

With the recent recognition that problems may occur following abrupt propranolol withdrawal, we reexamined hematologic data obtained in the course of our original study on the hemodynamic and clinical actions of the drug.<sup>1</sup>

The mechanism for the propranolol withdrawal effect is unknown and may be related to the multifactorial actions of the drug.<sup>11</sup> A likely explanation for the deterioration in exercise performance following drug withdrawal is the loss of sympathetic blockade of cardiovascular function resulting in an acute increase in myocardial oxygen demands in patients with angina pectoris.<sup>12</sup> Indeed 48 hours following propranolol cessation there was trace to no detectable drug in the blood. Others have documented lack of demonstrable sympathetic blockade at that time.<sup>13</sup> Increased angina may be related to greater



**Fig 3** Effects of placebo and its sudden withdrawal on ADP induced platelet aggregability in patients with angina pectoris. No changes in platelet sensitivity to ADP are seen during placebo therapy or after its abrupt withdrawal.



**Fig 4** Effects of placebo and its sudden withdrawal on epinephrine induced platelet aggregability in patients with angina pectoris. No changes in platelet sensitivity to epinephrine are seen during placebo therapy or after its abrupt withdrawal.

changes in frequency of angina were observed in placebo treated patients after withdrawal from placebo.

#### Discussion

Propranolol is an effective agent for treating patients with angina pectoris presumably because it reduces myocardial oxygen requirements

during exercise<sup>1,2</sup>. It allows the patient to do work while requiring less myocardial oxygen delivery thus delaying the onset of ischemia and the occurrence of chest pain<sup>1</sup>.

In this present study, a dramatic improvement in exercise performance was demonstrated during propranolol therapy in patients with angina pectoris associated with a significant decrease in

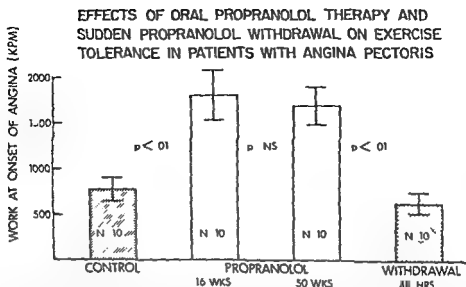


Fig 7 Effects of propranolol therapy and its sudden withdrawal on work performance in patients with angina pectoris. A significant mean increase in work performance occurs with propranolol therapy. Following abrupt cessation of propranolol, mean work performance returned to pretreatment levels. Work is measured in kilopond meters (k.p.m.)

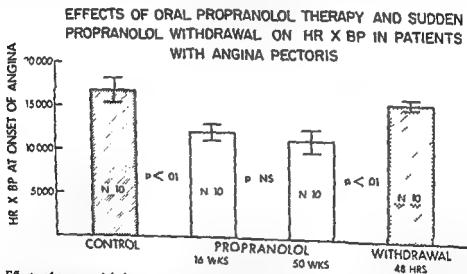
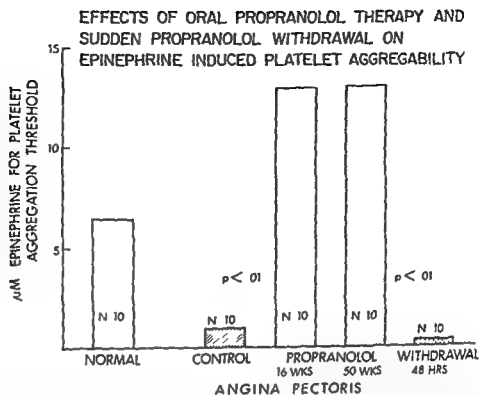


Fig 8 Effects of propranolol therapy and its sudden withdrawal on the heart rate-blood pressure product (HR x BP) in patients with angina pectoris. A significant decrease in the HR x BP at the onset of angina even though exercise level was higher after treatment is demonstrated after propranolol therapy. Following abrupt propranolol withdrawal the HR x BP increases to pretreatment levels.

Patients with angina pectoris demonstrated a significant hyperresponsiveness to aggregating concentrations of ADP and epinephrine. Propranolol significantly alters ADP and epinephrine induced platelet hyperaggregability towards normal, an effect which persists throughout the 50 week treatment period. Forty eight hours following propranolol withdrawal at a time when only

trace amounts of the drug were present in the serum, all patients had returned to their pretreatment hyperaggregable threshold levels. In six of 10 subjects, platelets were more hyperresponsive to aggregating concentrations of ADP and epinephrine than before any treatment. However, there was no association between the degree of rebound platelet hyperresponsiveness and the



**Fig 1** Effect of propranolol and its sudden withdrawal on epinephrine induced platelet aggregability in patients with angina pectoris. After propranolol platelets of treated patients are less sensitive to epinephrine (geometric mean) compared to before treatment and not significantly different from normal. Forty eight hours following abrupt propranolol withdrawal platelets of patients have returned to their pretreatment hyper responsiveness to epinephrine.

oxygen demands of the myocardium released from sympathetic blockade, but whether acute myocardial infarction is related to changes in sympathetic tone is unknown.

Decreased affinity of hemoglobin for oxygen and thus improved tissue availability of oxygen has been reported with propranolol therapy.<sup>6</sup> Abrupt withdrawal of treatment may possibly result in adverse alterations in oxygen affinity for hemoglobin. This finding however, has not been the case in our laboratory and we could not document changes in oxyhemoglobin dissociation in a small group of patients studied in our laboratory under other protocols.<sup>12</sup>

Another possible explanation for the occasionally serious manifestations of propranolol withdrawal may be related to the effects of the drug on platelet aggregation.<sup>1</sup> Propranolol in dosage sufficient to improve exercise tolerance has been demonstrated to restore towards normal the increased platelet aggregation noted in patients with angina pectoris.<sup>1</sup> Further work done in our laboratory has shown a specific platelet membrane effect of propranolol completely unrelated to its beta blocking properties.<sup>21</sup> Platelet aggrega-

tion was inhibited using concentrations of the drug that could be safely obtained in man.

If hyperaggregable platelets play a role in the pathogenesis of ischemic cardiovascular disease as has been suggested by many investigators,<sup>1</sup> an agent which reverses this abnormality may be an important adjunct in chronic treatment. At the same time abrupt discontinuation of the agent might trigger detrimental alteration of platelet function contributing to compromised coronary flow by obstruction of the microcirculation or accumulation of platelet aggregates on atheroma.

Myocardial infarction has been observed experimentally secondary to platelet aggregation, although the aggregates persisted for only a few minutes. Haerem<sup>22</sup> reported that platelet aggregates in the epicardial arteries of patients who died of cardiac causes were more numerous and extensive than those found in patients without cardiac disease. Yamazaki and colleagues,<sup>2</sup> Haft and Fani,<sup>23</sup> and others have suggested experimentally that hyperaggregable platelets may be playing an important role in ischemic cardiovascular events.

treatment. Prior to propranolol mean total work performance was  $765 \pm 125$  k p m. HR  $\times$  BP (heart rate blood pressure product) was  $16800 \pm 1535$ . Mean platelet aggregation threshold with ADP was  $132 \mu\text{M}^*$  with epinephrine  $126 \mu\text{M}^*$ . Patients treated with propranolol demonstrated significant improvement in exercise performance ( $1790 \pm 285$  k p m,  $p < 0.1$ ) reduction in HR  $\times$  BP ( $12000 \pm 895$ ,  $p < 0.1$ ) and an elevation in platelet aggregation threshold with ADP  $343 \mu\text{M}^*$  ( $p < 0.1$ ) with epinephrine  $129 \mu\text{M}^*$  ( $p < 0.1$ ). Following abrupt cessation of propranolol exercise tolerance and HR  $\times$  BP fell below pretreatment levels ( $630 \pm 117$  k p m and  $15500 \pm 513$  respectively). Similarly platelet aggregation threshold fell to  $10 \mu\text{M}^*$  with ADP and  $0.57 \mu\text{M}^*$  with epinephrine. In six patients platelets were significantly more hyperaggregable than prior to therapy. Anginal frequency increased in all but no acute infarction was observed. Abrupt withdrawal of propranolol may be deleterious in patients sometimes causing rebound platelet hyperaggregability associated with increasing anginal frequency and decreasing exercise tolerance.

The authors wish to extend a special note of appreciation to John Ferti, Ph.D., Professor of Statistics, Columbia University who assisted in the statistical evaluation of the data and to Dr Edmund Sonnenblick, Chief of Cardiology, Albert Einstein College of Medicine for his critical review of the manuscript and to Mrs Mary Senatore for her valuable help in preparing the manuscript.

Geometric mean

## REFERENCES

- Harrison D C. Beta adrenergic blockade 197. Pharmacology and clinical use. *Am J Cardiol* 29:432 1972.
- Prichard B N C and Cullum P M S. Assessment of propranolol in angina pectoris: clinical dose response curve and effect on electrocardiogram at rest and on exercise. *Br Heart J* 33:433 1971.
- Frishman W, Weksler M, Christodoulou J et al. Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. *Circulation* 50:887 1974.
- Miller R R, Olson H G, Amsterdam E A et al. Propranolol-withdrawal rebound phenomenon. *N Engl J Med* 293:416 1975.
- Alderman F L, Coltart D J, Wettach G E et al. Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 87:61 1974.
- Nellen M. Withdrawal of propranolol and myocardial infarct: a (Letter to Editor). *Lancet* 1:559 1973.
- Slone R. Withdrawal of propranolol and myocardial infarction (Letter to Editor). *Lancet* 2:156 1973.
- De Rombey J C, Freeman E et al. Withdrawal of propranolol and myocardial infarction (Letter to Editor). *Lancet* 1:1079 1973.
- Allen G, Genovese R. Propranolol withdrawal (Letter to Editor). *Ann Intern Med* 82:431 1975.
- Mizgala H F and Counsell J. Acute coronary syndromes following abrupt cessation of propranolol therapy (Abstr). *Circulation* 50 (Suppl II) II:235 1974.
- Frishman W, Weksler M, Christodoulou J et al. Platelet function in angina pectoris and beta blockade (Abstr). *Clin Res* 22:275 1974.
- Born G V F. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194:97 1962.
- Mustard J F, Hegardt R, Rosell H C et al. Effect of adenosine nucleotides on platelet aggregation and clotting time. *J Lab Clin Med* 64:548 1964.
- Arbarez R F, Freeman A H, Reichel P et al. The precordial electrocardiogram during exercise. *Circulation* 22:1090 1960.
- Robinson B F. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 35:1073 1967.
- Black J W, Duncan W A M and Shanks R G. Comparison of some properties of pronethalol and propranolol. *Br J Pharmacol* 25:577 1966.
- Coltart D J and Shand D G. Plasma propranolol levels in the qualitative assessment of beta adrenergic blockade in man. *Br Med J* 3:431 1970.
- Faulkner S L, Hopkins J T, Bourth R C et al. Time required for complete recovery from chronic propranolol therapy. *N Engl J Med* 289:607 1973.
- Frishman W H, Smith C N, Christodoulou J et al. Medical management of angina pectoris: multifactorial action of propranolol in coronary artery medicine and surgery. Norman J and Cooley D eds. chap 32. New York 1975. Appleton Century Crofts p 78.
- O'Keefe A, Miller L D, Delivoria Papadopoulos et al. Oxygen affinity in red cells changes induced by propranolol. *Science* 175:1372 1972.
- Weksler B B and Pank J. Propranolol as a modifier of platelet function by membrane action (Abstr). *Clin Res* 23:284 1975.
- Yamazaki H, Kobayashi I and Shunamoto T. Enhancement of ADP induced platelet aggregation by exercise test in coronary patients and its prevention by pyridinocarbamate. *Thromb Diath Haemorrh* 24:438 1970.
- Mustard J F. Platelets and thrombosis in acute myocardial infarction. *Hospital Practice* 7:115 1972.
- Hafiz J I and Fani K. Stress and the induction of intravascular platelet aggregation in the heart. *Circulation* 48:164 1973.
- Haerem J W. Sudden coronary death: the occurrence of platelet aggregates in the epicardial arteries of man. *Atherosclerosis* 14:417 1971.
- Hoak J C, Warner E D and Connor W M. Platelets, fatty acids and thrombosis. *Circ Res* 20:11 1967.
- Schwartz C J, Warner F D and Connor W F. Catecholamine and platelet aggregation. *Circ Res* 21 (Suppl. III) III:187 1967.
- Hafiz J I, Gershengorn H, Krän P et al. Protection of epinephrine induced myocardial necrosis by drugs that inhibit platelet aggregation. *Am J Cardiol* 30:838 1972.
- Harrison M J, Fennell P R and Mitchell J H. The variability of human platelet aggregation. *J Atheroscler Res* 7:19 1967.
- Marcus A J. Platelet function. *N Engl J Med* 280:1213 1978 and 1330 1976.

**Table II** Effects of placebo and propranolol therapy and abrupt treatment withdrawal in patients with angina pectoris

|             | Patients age |            |       | Propranolol blood levels (ng/ml) | Exercise                     |                                    | Platelet aggregation |             |
|-------------|--------------|------------|-------|----------------------------------|------------------------------|------------------------------------|----------------------|-------------|
|             | No           | Mean (yr.) | Sex   |                                  | Total work (kilopond meters) | Heart rate blood pres sur. product | ADP $\mu$ M          | Epi $\mu$ M |
|             |              |            |       |                                  |                              |                                    |                      |             |
| Placebo     |              |            |       |                                  |                              |                                    |                      |             |
| Control     | 10           |            | 6M 4F | II                               | 866 $\pm$ 122                | 16 000 $\pm$ 467                   | 1.78                 | 1.40        |
| 16 weeks    | 10           | 52         |       | II                               | 933 $\pm$ 136                | 16 333 $\pm$ 416                   | 1.78                 | 1.40        |
| 50 weeks    | 10           |            |       | 0                                | 883 $\pm$ 113                | 16 344 $\pm$ 383                   | 1.55                 | 1.40        |
| Withdrawal  | 10           |            |       | III                              | 840 $\pm$ 136                | 15 700 $\pm$ 484                   | 1.55                 | 1.37        |
| Propranolol |              |            |       |                                  |                              |                                    |                      |             |
| Control     | 10           |            | 6M 4F | 0                                | 765 $\pm$ 125                | 16 800 $\pm$ 1 540                 | 1.32                 | 1.07        |
| 16 weeks    | 10           | 54         |       | 54.8 $\pm$ 9.2                   | 1 790 $\pm$ 285              | 12 000 $\pm$ 885                   | 3.43                 | 12.90       |
| 50 weeks    | 10           |            |       | 47.6 $\pm$ 8.4                   | 1 690 $\pm$ 200              | 11 200 $\pm$ 1 300                 | 4.90                 | 13.20       |
| Withdrawal  | 10           |            |       | 1 $\pm$ 8                        | 630 $\pm$ 117                | 15 500 $\pm$ 513                   | 1.00                 | 0.57        |

Geometric mean

extent of deterioration in exercise performance or frequency of angina attacks in specific patients following propranolol withdrawal

The exact mechanism of platelet hyperaggregability after acute propranolol withdrawal is not known. One could speculate that platelet hyperaggregability may have been related to increased *in vivo* catecholamine levels or increased sensitivity of platelets to catecholamines, changes in free fatty acid levels<sup>28</sup> or a change in the platelet membrane morphology following disappearance of the drug from the blood. Catecholamines have known effect on platelet function<sup>1, 29</sup> and the anxiety associated with the removal of effective therapy may have influenced the results. Catecholamine levels were not measured in this study, so that this possibility cannot be totally excluded. However, propranolol treated patients withdrawn to placebo appeared no different from patients withdrawn to no therapy and placebo withdrawn patients did not appear more hyperresponsive.

As previously described,<sup>3</sup> repeated measurements of human platelet aggregation induced by ADP and epinephrine can be influenced by many patient variables. The technique of blood sampling and processing and the rapidity in which platelet studies are performed is critically important.<sup>29</sup> Since many drugs influence platelet function studies<sup>30</sup> this factor must be rigidly controlled. In this study, considerable effort was devoted to minimizing those patient variables influencing platelet function testing.

Whatever the mechanism for the propranolol

withdrawal phenomenon it is clear that beneficial effects of the drug sympathetic blockade, improvement in exercise tolerance and normalization of platelet aggregability have disappeared by 48 hours following cessation of propranolol therapy. Furthermore, in some patients there is increased platelet hyperaggregability after drug withdrawal.

Further work is needed to determine whether platelet hyperresponsiveness continues beyond 48 hours, and if so, for how long, and whether subjects with increased ischemia or infarction are those with the most prominent or long standing effects on platelet aggregability. Finally, studies are needed to determine platelet behavior with gradual withdrawal of propranolol as well as the clinical and rheologic implications of adding other agents such as aspirin to block platelet hyperaggregability in this situation.

### Summary

Data collected before the initial reports of myocardial infarction following sudden withdrawal of propranolol are presented here to evaluate possible mechanisms for this phenomenon. Twenty patients with angina pectoris were randomized into placebo and propranolol (160 mg/day) treated groups and followed for 50 weeks at which time treatment was abruptly discontinued. Measurements of exercise tolerance (the product of heart rate and blood pressure at exercise end point (HR  $\times$  BP)) and platelet aggregation thresholds in response to ADP and epinephrine were made before, during and after

treatment. Prior to propranolol mean total work performance was  $76.0 \pm 125$  kpm HR  $\times$  BP (heart rate blood pressure product) was  $16800 \pm 153$ . Mean platelet aggregation threshold with ADP was  $132 \mu\text{M}^*$  with epinephrine  $126 \mu\text{M}^*$ . Patients treated with propranolol demonstrated significant improvement in exercise performance ( $1790 \pm 285$  kpm  $p < 0.1$ ) reduction in HR  $\times$  BP ( $12000 \pm 890$   $p < 0.1$ ) and an elevation in platelet aggregation threshold with ADP  $343 \mu\text{M}^*$  ( $p < 0.1$ ) with epinephrine  $129 \mu\text{M}^*$  ( $p < 0.1$ ). Following abrupt cessation of propranolol exercise tolerance and HR  $\times$  BP fell below pretreatment levels ( $630 \pm 117$  kpm and  $15500 \pm 513$  respectively). Similarly platelet aggregation threshold fell to  $10 \mu\text{M}^*$  with ADP and  $0.57 \mu\text{M}^*$  with epinephrine. In six patients platelets were significantly more hyperaggregable than prior to therapy. Anginal frequency increased in all but no acute infarction was observed. Abrupt withdrawal of propranolol may be deleterious in patients sometimes causing rebound platelet hyperaggregability associated with increasing anginal frequency and decreasing exercise tolerance.

The authors wish to extend a special note of appreciation to John Ferrig Ph.D. Professor of Statistics, Columbia University who assisted in the statistical evaluation of the data and to Dr Edmund Sonnenblick, Chief of Cardiology, Albert Einstein College of Medicine for his critical review of the manuscript and to Mrs Mary Senatore for her valuable help in preparing the manuscript.

From the m m

## REFERENCES

- Harrison D C. Beta adrenergic blockade 1979. Pharmacology and clinical use. *Am J Cardiol* 29:432 1979.
- Frishman B N C and Williams P M S. Assessment of propranolol in angina pectoris: clinical dose response curve and effect on electrocardiogram at rest and on exercise. *Br Heart J* 33:473 1971.
- Frishman W, Weksler B, Christodoulou J et al. Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. *Circulation* 50:887 1974.
- Miller R R, Olson R C, Amsterdam E A et al. Propranolol-withdrawal rebound phenomenon. *N Engl J Med* 293:416 1975.
- Alderman F L, Coltart D J, Wettach G E et al. Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 87:62 1974.
- Nellen M. Withdrawal of propranolol and myocardial infarction (Letter to Editor). *Lancet* 1:558 1973.
- Slone R. Withdrawal of propranolol and myocardial infarction (Letter to Editor). *Lancet* 1:556 1973.
- Diaz R, Somberg J C, Freeman E C et al. Withdrawal of propranolol and myocardial infarction (Letter to Editor). *Lancet* 1:1068 1973.

- Allen R, Genovese B. Propranolol withdrawal (Letter to Editor). *Ann Intern Med* 82:431 1975.
- Mizgala H F and Counsell J. Acute coronary syndromes following abrupt cessation of propranolol therapy (Abstr). *Circulation* 50 (Suppl II) II:235 1974.
- Frishman W, Weksler B, Christodoulou J et al. Platelet function in angina pectoris and beta blockade (Abstr). *Clin Res* 22:275 1974.
- Born C V R. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194:97 1962.
- Mustard J F, Hegardt R, Rosell H C et al. Effect of adenosine nucleotides on platelet aggregation and clotting time. *J Lab Clin Med* 64:549 1964.
- Arborelius R F, Framan A H, Reichel F et al. The precordial electrocardiogram during exercise. *Circulation* 22:1060 1960.
- Robinson B F. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 35:1073 1967.
- Black J W, Duncan W A M and Shanks R D. Comparison of some properties of pronethalol and propranolol. *Br J Pharmacol* 26:577 1969.
- Coltart D J and Shand D G. Plasma propranolol levels in the qualitative assessment of beta adrenergic blockade in man. *Br Med J* 3:731 1970.
- Faulkner S L, Hopkins J T, Borth R C et al. Time required for complete recovery from chronic propranolol therapy. *N Engl J Med* 289:607 1973.
- Frishman W H, Smith C, Christodoulou J, et al. Medical management of angina pectoris: multifactorial action of propranolol in coronary artery medicine and surgery. Norman J and Cooley D eds. chap 37. New York, 1973. Appleton Century Crofts, 285.
- Okin F A, Miller L D, Delivoria Papadopoulos et al. Oxygen affinity in red cells: changes induced by propranolol. *Science* 175:13 2 1972.
- Weksler B B and Pink J. Propranolol as a modifier of platelet function by membrane action (Abstr). *Clin Res* 23:284 1975.
- Yamazaki H, Kobayashi I, and Shimamoto T. Enhancement of ADP induced platelet aggregation by exercise test in coronary patients and its prevention by pyridinolcarbamate. *Thromb Diath Haemorrh* 24:438, 1970.
- Mustard J F. Platelets and thrombosis in acute myocardial infarction. *Hospital Practice* 7:115, 1972.
- Hoff J I and Fan K. Stress and the induction of intravascular platelet aggregation in the heart. *Circulation* 48:164 1973.
- Haerem J W. Sudden coronary death: the occurrence of platelet aggregates in the epicardial arteries of man. *Atherosclerosis* 14:417 1971.
- Hoak J C, Warner E D and Connor W E. Platelets fatty acids and thromboxane. *Circ Res* 20:11 1967.
- Schwartz C J, Warner E D and Connor W E. Catecholamine and platelet aggregation. *Circ Res* 21 (Suppl III) III:187 1966.
- Hoff J I, Gershengorn K, Hranz P et al. Protection of epinephrine induced myocardial necrosis by drugs that inhibit platelet aggregation. *Am J Cardiol* 30:638 1972.
- Harrison M J, Emmon P R and Mitchell J R. The variability of human platelet aggregation. *J Atheroscler Res* 7:197 1967.
- Marcus A J. Platelet function. *N Engl J Med* 280 pp 1713 178 and 1430 1969.



# The variability of arterial pressure

W A Littler, MD, MRCP\*  
M J West MB PhD, MRACP\*\*  
A J Honour MA DPhil\*\*\*  
P Sleight MD FRCP\*\*\*\*  
Oxford England

The decision to treat patients with high blood pressure depends largely on the level of pressure. It is therefore important to obtain data from the patient that is truly representative of his average arterial pressure. A major difficulty in evaluating such data is the great variability in the level of blood pressure in any individual patient. Previous workers have attempted to solve the problem by the measurement of blood pressure under standard conditions for example at rest and on repeated occasions so as to obtain a representative pressure.<sup>1</sup> The relationship between the indirectly obtained casual blood pressure and the average 24 hour blood pressure sustained by the circulation over 24 hours, is unknown.

Over the last ten years there have appeared from this laboratory a series of publications describing the development and application of a system for continuously recording direct arterial pressure in unrestricted patients.<sup>2</sup> It has now become possible to analyze data collected over a 24 hour period quantitatively in a great deal more depth than was hitherto possible and this paper describes our experience with the latest develop-

ment of this technique and its use in evaluating the variability of arterial pressure over a 24 hour period.

## Patients and methods

Ten patients are included in this study. After informed consent all had their arterial pressure recorded over a 24 hour period as previously described.<sup>3</sup> The details of the ten patients are listed in Table I and all were asymptomatic and none was receiving drug therapy. All ten patients went about their normal daily activities during the course of the study and they slept at home.

**Tape analysis system** This system was developed in conjunction with our Departments by the Engineering Division of AERE Harwell Berkshire. The system consists of three separate units: (a) a tape replay unit, (b) a blood pressure histogram plotter and (c) a multi channel analyzer.

The histogram plotter accepts the output for the tape replay unit (speed set at 25 times the recording speed) and derives data in digital form of systolic diastolic and mean pressures and measures pulse interval all on a beat to beat basis. The data are held in four registers which sequentially address the memory of the multi channel analyzer at the end of each beat. When the memory is addressed the contents stored at that address are incremented so that a frequency distribution histogram of each of the four parameters builds up. Each parameter is allocated 128 channels in the store of the multichannel analyzer. Each channel size representing 2.5 mm Hg. When the analysis is complete the elements of the four frequency distribution histograms are discharged via a teletypewriter on to paper.

From the University Department of Cardiovascular Medicine University of Oxford and Radcliffe Infirmary Oxford England  
Received for publication Sept 16 1976  
Accepted for publication Feb 23 1977

Reprint requests Professor W A Littler British Heart Foundation Department of Cardiology East Birmingham Hospital Bordesley Green East Birmingham B9 5ST England

Lecturer University Department of Cardiovascular Medicine University of Oxford and Radcliffe Infirmary

Research Fellow University Department of Cardiovascular Medicine University of Oxford and Radcliffe Infirmary

First Assistant University Department of the Regius Professor of Medicine University of Oxford and Radcliffe Infirmary

Professor University Department of Cardiovascular Medicine University of Oxford and Radcliffe Infirmary

punch tape and these data are subsequently submitted to standard statistical analysis by computer program. For each histogram the mean, variance and standard deviation were determined. It is important to scrutinize the complete 24 hour recording before feeding it through this system in order to avoid inaccurate information due to technical faults or error in the recording procedure. The accuracy of this automatic analysis was checked against the direct measurements of the records by two independent observers. These two observers agreed with one another with an accuracy of  $\pm$  or  $\pm 4$  per cent and the within observer error was  $\pm$  or  $\pm 1$  per cent. Compared with this manual analysis the automatic system corresponded with an accuracy of  $\pm$  or  $\pm 6$  per cent for arterial pressure and heart rate and  $\pm$  or  $\pm 3$  per cent for the total number of beats analyzed. The degree of agreement between observer and machine was much greater during the period of sleep when the error was reduced by approximately 50 per cent.

**Analysis of individual records.** Records of the ten individual patients were analyzed beat by beat on an hourly basis throughout the 24 hour period. In addition the waking and sleeping periods were each averaged, sleep being taken as that period from the time that the subject indicated that he was in bed until the time that he was awake again.

**Statistical methods.** To test whether the variability of systolic pressure differed from that of diastolic pressure throughout the day and night the Wilcoxon matched pairs signed ranks test was employed. Variability was determined from the standard deviation about the mean for each hour.

## Results

**Frequency distribution of blood pressure over 24 hours.** The frequency distribution pattern of arterial pressure over 24 hours described a bimodal curve (Fig. 1) in all but one patient (Case 10). The bimodality was uninfluenced by the over all average pressure. The lower mode was due predominantly to the fall of pressure which occurs during sleep (Fig. 2). The length of sleep was the single most important factor in determining the shape of the frequency distribution curve (Fig. 3).

**The variability of arterial pressure.** Variability

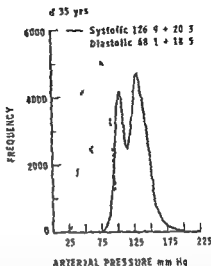


Fig. 1 A frequency distribution curve of systolic and diastolic blood pressure in a 35-year old normotensive individual (Case 8). Note the bimodality of both systolic and diastolic pressure and the wide range of pressures covered throughout the 24 hour period.

Table 1 Details of 10 patients selected to give a range of different levels of arterial pressure

| Case | Sex | Age | BSA | Casual BP (mm Hg) | CXR    | ECG    | Bio chemical profile |
|------|-----|-----|-----|-------------------|--------|--------|----------------------|
| 1    | F   | 53  | 1.8 | 200/90            | Normal | LV+    | Normal               |
| 2    | M   | 60  | 1.8 | 180/105           | Normal | Normal | Normal               |
| 3    | F   | 8   | 1.6 | 160/110           | Normal | LV+    | Normal               |
| 4    | M   | 26  | 1.9 | 130/100           | Normal | Normal | Normal               |
| 5    | F   | 32  | 1.5 | 130/80            | Normal | Normal | Normal               |
| 6    | F   | 23  | 1.5 | 180/110           | Normal | Normal | Normal               |
| 7    | F   | 44  | 1.5 | 160/100           | Normal | Normal | Normal               |
| 8    | M   | 35  | 2.0 | 120/70            | Normal | Normal | Normal               |
| 9    | M   | 21  | 1.8 | 130/90            | Normal | Normal | Normal               |
| 10   | M   | 20  | 1.7 | 165/110           | Normal | Normal | Normal               |

BSA = body surface area, CXR = chest radiograph.

of arterial pressure was determined in ten patients from the standard deviation of pressure about the mean for each hour (example Fig. 4). Throughout the 24 hour period systolic pressure variation was significantly greater than that in diastolic pressure in all but Case 3 in whom there was no difference. This variability was most acutely affected by physical exertion although in individual instances there was marked change in pressure in response to psychological influences. During sleep systolic and diastolic pressures both

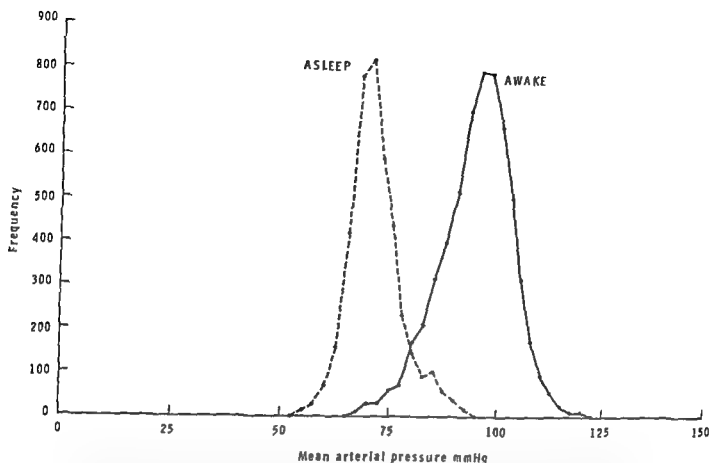


Fig 2 A frequency distribution plot of mean arterial pressure for two separate hours in the day (Case 8) (i) A one hour period during sleep and (ii) a one hour period during waking when the patient was for the majority of the time sitting quietly and not engaged in physical activity. Note that during sleep pressure is lower and covers a smaller range than during the waking period.

Table II Summary of awake and asleep arterial pressures in the 10 patients whose records were analyzed on an hourly basis

| Case | Awake    |    |           |    |       |    | Asleep   |    |           |    |      |    |
|------|----------|----|-----------|----|-------|----|----------|----|-----------|----|------|----|
|      | Systolic | SD | Diastolic | SD | Mean  | SD | Systolic | SD | Diastolic | SD | Mean | SD |
| 1    | 216      | 26 | 108       | 12 | 145   | 15 | 122      | 13 | 70        | 7  | 92   | 7  |
| 2    | 140      | 15 | 109       | 12 | 127   | 11 | 110      | 8  | 90        | 7  | 102  | 8  |
| 3    | 138      | 18 | 91        | 11 | 106   | 9  | 112      | 8  | 79        | 5  | 92   | 6  |
| 4    | 144      | 29 | 63        | 22 | 94    | 20 | 105      | 14 | 49        | 16 | 75   | 15 |
| 5    | 182      | 26 | 115       | 15 | 141   | 16 | 132      | 11 | 81        | 7  | 103  | 8  |
| 6    | 131      | 13 | 124       | 11 | 132   | 11 | 109      | 7  | 92        | 7  | 105  | 7  |
| 7    | 99       | 14 | 72        | 21 | 86    | 17 | 79       | 7  | 40        | 9  | 58   | 7  |
| 8    | 188      | 20 | 88        | 11 | 122   | 13 | 170      | 12 | 72        | 6  | 109  | 8  |
| 9    | 180      | 14 | 126       | 10 | 149   | 11 | 156      | 11 | 123       | 8  | 140  | 7  |
| 10   | 141      | 20 | 44        | 13 | 95    | 13 | 116      | 17 | 55        | 11 | 70   | 12 |
| Mean | 155.9    |    | 97.0      |    | 119.7 |    | 121.8    |    | 75.9      |    | 96.1 |    |

fell by an average of 20 per cent of the waking pressure and were significantly less variable than during waking. During sleep systolic pressure was still significantly more variable than diastolic pressures.

Spontaneous fluctuations of pressure occurred

approximately every 90 to 120 minutes during sleep (Fig 5) and accounted for the greatest variability during this period being probably due to periods of rapid eye movement (REM) sleep. An alternative explanation for this rhythmicity could be that these fluctuations reflect the

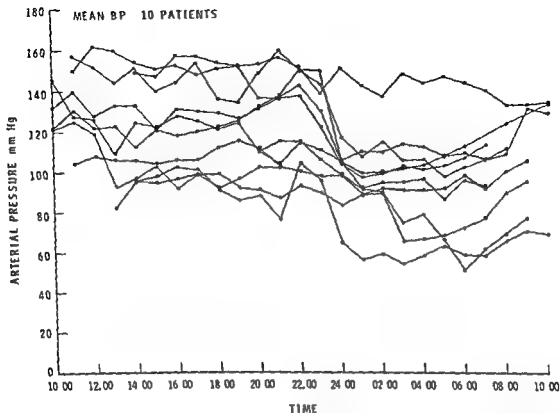


Fig 3 A plot of mean arterial pressure (diastolic pressure plus a third of the pulse amplitude) for ten patients. This emphasises the fall in arterial pressure during sleep in all but one subject (Case 10) and this individual did not sleep very well during the period of study which is reflected in the arterial pressure which was maintained at a similar level to that during waking.

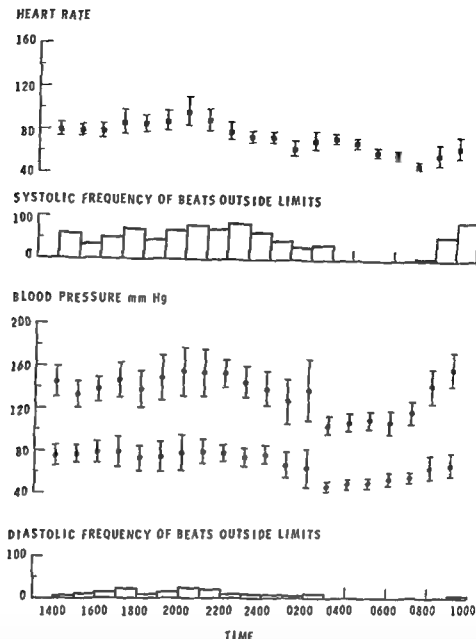
changes in arterial pressure produced by respiration.

#### Discussion

The development of systems for continuously recording arterial pressure has enabled us to obtain a more accurate characterization of an individual's blood pressure during his normal daily activities and thus avoid the pitfalls that may occur due to the presence of the orientating or defence reflex. The automatic analysis system makes it possible to measure each individual beat during the 24 hour period and obtain quantitative data useful in the assessment of hypotensive therapy. The results in a group of patients studied before and after beta blockade will form the basis of a separate publication. Since sleep produces similar percentage falls in pressure irrespective of the over all level in arterial pressure it is perhaps not surprising that drug therapy which lowers

blood pressure does not apparently alter this bi-modality. Patients who did not sleep very well or at all did not demonstrate this bi-modality.

Systolic pressure shows much more variation during the day and night when compared with diastolic pressure and the higher the level of systolic pressure the greater was the variability. This may reflect the poorer baroreflex control found in hypertension. Sokolow and associates<sup>9</sup> using frequent semiautomatic blood pressure recordings taken by the ambulatory patient away from the medical environment have shown that although the prevalence of hypertensive complications increases as the casual pressure increases the portable diastolic pressure tends to be more predictive of severity class than does the casual diastolic pressure. Whether or not the variations in systolic pressure are of themselves important in determining the degree of target organ damage cannot be answered by the present study and will



**Fig 4** A plot of systolic and diastolic pressure against time in an individual patient. Pressures have been averaged for each hour and plotted with its standard deviation. Note that during waking the pressure is higher and more variable (as indicated by the larger standard deviations) than during sleep. In addition in this diagram the frequency of those beats above the arbitrary limits of 140 systolic and 90 diastolic have also been plotted.

require longitudinal studies on the same patient over a large number of years. A recent report of the Framingham Study<sup>10</sup> appears to confirm the importance of systolic hypertension as a risk factor in cardiovascular disease—systolic pressure being a stronger determinant for the risk of coronary heart disease than either diastolic or mean blood pressure in women and in men over 45 years of age. It appeared to be independent of other variables and to retain its importance when subjects with other risk factors for coronary artery disease were excluded from analysis. Kannel<sup>10</sup> has suggested that systolic hypertension

may accelerate atherogenesis or may reflect an increased susceptibility to atherogenesis due to an altered state of the arterial wall while Page and Sidd<sup>11</sup> have suggested an alternative explanation that is that it may simply reflect advancing atherogenesis in the absence of other known risk factors.

We have found that the casual blood pressures measured in outpatient clinics tended to be higher than the average 24 hour pressure recorded by our method in some 60 per cent of patients. This is not surprising since our average 24 hour figure would include the period while the patient was

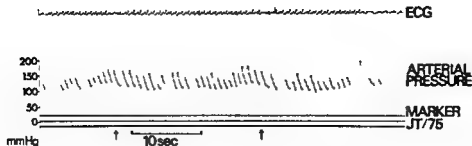


Fig 5 A record from a young woman (Case 6) obtained during sleep. It shows both the electrocardiogram and the arterial pressure. There are marked spontaneous increases in arterial pressure occurring in rhythmic fashion during this period of sleep. Note the marked slowing associated with this rise in pressure. (This pattern we believe is an example of baroreflex activity during sleep buffering an initial sympathetically mediated rise in blood pressure.)

asleep and exclude the alerting response to an observer whereas casual recordings are invariably taken during the waking period which necessitate the presence of an observer. This finding has been shown on several occasions previously. Furthermore Sokolow and colleagues<sup>9</sup> found that the presence of target organ damage related more closely to the average pressure for the 24 hours than to the casual blood pressure. We have not attempted such a comparison in our small group of patients reported here but in a previous publication we have shown that the averaged 24 hour blood pressure in patients with high casual levels and little evidence of target organ damage was significantly lower than the average casual readings over several months and furthermore indicated the use of this type of assessment in patients who are difficult to diagnose because of the great variability of their arterial pressure.

### Summary

Direct arterial pressure has been recorded continuously on magnetic tape in totally unrestricted patients going about their normal routine outside hospital for periods of 24 hours.

On replaying these tapes data are derived in digital form of systolic diastolic and mean pressure plus pulse interval all on a beat by beat basis a computer program then performs averaging and statistical analysis of these data.

The frequency distribution of blood pressure over a 24 hour period was plotted and showed a bimodal curve the lesser mode being due predominantly to sleep. This bimodality was

unaffected by the average 24 hour pressure but was modified by the length of sleep.

The variability of arterial pressure was determined from the standard deviation by averaging pressure over each hour in 10 patients (five men five women). They were selected to give a range of different levels of arterial pressure and had never received drugs. Throughout the 24 hours the variability of systolic pressure was significantly greater than that in diastolic pressure. This variability was most acutely affected by physical exercise.

During sleep both systolic and diastolic pressure fell by an average of 20 per cent of the waking pressure and both were less variable than during waking. Spontaneous rhythmic changes of pressure occurring approximately every 90 to 120 minutes accounted for the greatest variability during sleep and were probably due to REM sleep.

### REFERENCES

- 1 Pickering G W. High blood pressure. London 1968 J & A Churchill Ltd.
- 2 Bevan A T, Honour A J and Stott M D. Direct arterial pressure recording in unrestricted man. Clin Sci 36 379 1969.
- 3 Lattier W A, Honour A J and Sleight P. Continuous recording of direct arterial pressure and electrocardiogram in unrestricted man. Br Med J 3 76 1972.
- 4 Snedecor G W and Cochran W G. Statistical methods. Ames Iowa 1967 The Iowa State College Press p 81.
- 5 Siegel S. Non parametric statistics. New York 1956 McGraw Hill Book Company p 75.
- 6 West M J. Ambulatory monitoring of the intra arterial blood pressure: application in the clinical trial of a new hypotensive agent. (Unpublished data).

- 7 Littler W A Honour A J Carter R D and Sleight P Sleep and blood pressure *Br Med J* **3** 346 1975
- 8 Gribbin B Pickering T G Sleight P and Peto R Effect of age and high blood pressure on baroreflex sensitivity in man *Circ Res* **29** 424 1971
- 9 Sokolow M Werdegar D Kain H K and Hinman A T Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension *Circulation* **34** 279 1966
- 10 Kannel W B Role of blood pressure in cardiovascular morbidity and mortality *Progr Cardiovasc Dis* **17** 5 1974
- 11 Page L H and Sidd J J Medical management of primary hypertension *N Engl J Med* **287** 1018 1972
- 12 Irving J H Kerr F Ewing D J and Kirby B J Value of prolonged recording of blood pressure in assessment of hypertension *Br Hrt J* **36** 859 1974
- 13 Littler W A Honour A J Pugsley D J and Sleight P Continuous recording of direct arterial pressure in unrestricted patients Its role in the diagnosis and management of high blood pressure *Circulation* **51** 1101 1975

# The systolic time intervals in thyroid dysfunction

Dietrich Burckhardt MD  
Jean Jacques Staub MD  
Martin Kraenzlin MD  
Ernst Raeder MD  
Urs Engel MD  
Peter Cloppenburg MD

*With the technical assistance of Priska Boschung  
Basel Switzerland*

Cardiovascular changes in thyroid disease are a well known fact since thyroid hormones have a positive chronotropic and inotropic action. Heart rate, maximum velocity of fiber shortening rate of rise of left ventricular pressure (LV dp/dt) and cardiac output are therefore increased in patients with hyperthyroidism. In hypothyroidism all these parameters are reduced.<sup>\*</sup> Non-invasive techniques such as the systolic time intervals (STI) allow us to assess myocardial contractility because they correlate with LVdp/dt and stroke volume. The time intervals can easily be obtained by simultaneous recording of the electrocardiogram (ECG), carotid pulse tracing and phonocardiogram. Being inexpensive and carrying no risks, the investigation can be performed repeatedly and yields immediate results.

The purpose of this study was to investigate the value of the STI in the diagnosis of hyper- and hypothyroidism and to evaluate the correlation between thyroid function and STI.

Furthermore we assessed the value of the STI as a follow-up examination during treatment of thyroid dysfunction.

Finally the accuracy of another frequently used non-invasive test, namely the Achilles reflex time, was compared with that of the STI.

## Methods

**Patient selection** Between June 1974 and June 1975 53 patients (34 women and 19 men) with a mean age of  $44 \pm 17$  years (range 19 to 80 years) with signs or symptoms suggesting thyroid dysfunction were investigated and thyroid function tests as well as 75 STI were obtained. Patients with congestive heart failure, arterial hypertension, atrial fibrillation or flutter, old myocardial infarction or abnormal cardiac findings in their chest x-ray were excluded from the study. None of the patients received cardioactive drugs such as digitalis,  $\beta$ -adrenergic blocking agents or other medications with possible effects on myocardial contractility or peripheral resistance.

The complete endocrine investigation disclosed 17 patients with hyperthyroidism before treatment (10 patients with toxic diffuse goiter (Graves disease), four with toxic multinodular goiter, two with toxic multinodular goiter and one patient with exogenous thyroid hormone excess). Eight subjects had primary hypothyroidism. In 15 cases a euthyroid state was proven.

Four hyperthyroid patients were followed one or several times during treatment with carbimazole and three hypothyroid patients were followed during substitution with increasing doses of thyroid hormones.

**Thyroid studies** On the basis of two or more thyroid tests and response to treatment we made a classification into seven groups (see Table I).

From the Kantonal Hospital Basel, Department of Internal Medicine, University of Basel, Switzerland.

Received for publication Oct. 5, 1975.

Accepted for publication in Dec. 13, 1975.

Reprint requests: Dr. Burckhardt MD, Medizinische Poliklinik, Kantonsspital CH-4056 Basel, Switzerland.



**Table 1** Laboratory values for serum thyroxine (T<sub>4</sub>) and free T<sub>4</sub> Index (FT<sub>4</sub>I) in the different groups of patients, excluding patients with isolated T<sub>4</sub> hyperthyroidism

|                  | T (μg/100 ml)<br>(mean ± 1 SD) | FT <sub>4</sub> I<br>(mean ± 1 SD) |
|------------------|--------------------------------|------------------------------------|
| Group 1 (n = 13) | 8.9 ± 1.8                      | 8.7 ± 1.9                          |
| Group 2 (n = 8)  | 22.6 ± 6.6                     | 31.9 ± 12.8                        |
| Group 3 (n = 7)  | 20.3 ± 4.6                     | 23.1 ± 6.8                         |
| Group 4 (n = 13) | 8.8 ± 3.1                      | 8.1 ± 3.1                          |
| Group 5 (n = 3)  | 2.4 ± 1.8                      | 3.3 ± 2.3                          |
| Group 6 (n = 7)  | 3.5 ± 1.2                      | 3.5 ± 1.4                          |
| Group 7 (n = 12) | 9.2 ± 2.4                      | 8.8 ± 2.4                          |

Normal values for T<sub>4</sub> = 6 to 12 μg/100 ml

† Normal values for FT<sub>4</sub>I = 4.0 to 15.4

Patients could reappear in another group after treatment

#### 1 Euthyroid (n = 15)

Serum thyroxine (modification of Murphy and Pattee<sup>1</sup>) and free T<sub>4</sub> Index (FT<sub>4</sub>I) within normal range

Normal T<sub>4</sub> (radioimmunoassay modification of Hesch and Evelett<sup>2</sup>)

Normal TRH stimulation test\* (according to Straub and associates<sup>3,4</sup>)

These patients served as normal controls. Their STI were comparable to the normal values published by Weissler and colleagues

#### 2 Hyperthyroid without treatment (n = 11)

Elevated serum thyroxine and FT<sub>4</sub>I and/or elevated T<sub>4</sub> and/or abnormal TRH test (delta TSH < 20 μU/ml)†

#### 3 Still hyperthyroid on treatment (n = 7)

Elevated serum thyroxine and FT<sub>4</sub>I and/or elevated T<sub>4</sub> with suppressed TSH after TRH

#### 4 Previous hyperthyroidism euthyroid on treatment (n = 13)

Normal serum thyroxine and FT<sub>4</sub>I and normal T<sub>4</sub> and/or normal TRH test (this test was evaluated only if TSH could be stimulated)

#### 5 Hypothyroid without treatment (n = 4)

Reduced serum thyroxine and FT<sub>4</sub>I and abnormal TRH test (elevated basal TSH and/or exaggerated response to TRH)

A normal TRH test rules out any form of hyper- or hypothyroidism

† TSH after stimulation with TRH is equally suppressed in patients with mild and severe hyperthyroidism

#### 6 Still hypothyroid on treatment (n = 11)

Abnormal TRH test (elevated basal TSH and/or exaggerated response to TRH)

#### 7 Previous primary hypothyroidism euthyroid on treatment (n = 14)

Normal TRH test\*

**Systolic time intervals (STI)** The systolic time intervals were measured in supine position at least 2 hours postprandially after a 10 minute period of rest. Electrocardiogram (Lead II) phonocardiogram and carotid pulse tracing were recorded simultaneously on a Hellige six channel recorder (multiscriptor 9400/6) with a paper speed of 100 mm/sec. The following intervals were measured directly.

a Left ventricular ejection time (LVET) as the interval between the beginning of the initial upstroke and the trough of the incisural notch of the carotid pulse tracing

b The total electromechanical systole (QS) as the interval between the beginning of the Q wave in the electrocardiogram and the first high frequency vibration of the aortic component of the second heart sound

From the above measurements the prejection period (PEP) was calculated by subtracting LVET from QS

The isovolumic contraction time was not measured because of difficulties in clearly delineating the beginning of the first heart sound in several instances

The values for LVET and PEP were corrected for a hypothetical heart rate of zero using the regression equations of Weissler and associates<sup>5</sup> and then designated with the subscript c

In all patients the ratio LVET<sub>c</sub>/PEP<sub>c</sub> was calculated. In 33 patients, the Achilles reflex time and PEP were determined simultaneously to permit comparison

For the statistical analyses the Student's t test was used. The correlations were calculated and plotted with a Hewlett Packard computer

All data are reported as mean ± 1 SD

#### Results

1 STI in patients with hyperthyroidism. In patients with hyperthyroidism (untreated or on treatment Groups 2 and 3) PEP<sub>c</sub> was shortened significantly (89.8 ± 12.3 msec and 94.7 ± 8.3 msec, respectively compared to a control of 118.0 ± 9.3 msec (p < 0.0005) see Fig 1). Although to a lesser degree this was also true for

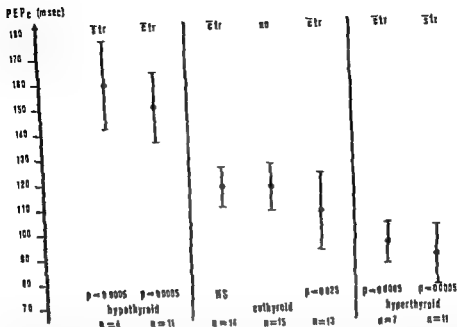


Fig 1 The corrected pre-ejection period (PEPc) shows a significant prolongation in hypothyroid patients but is shortened in hyperthyroidism. Patients with successfully treated hyperthyroidism (euthyroid on treatment) had still a somewhat shortened PEPc values represent significance of the patient group when compared with the group of normal controls (no). NS = not significant. Ttr = without treatment. Etr = on treatment.

patients with previous hyperthyroidism (Group 4 PEP =  $107.7 \pm 14.8$  msec) LVET was only slightly and insignificantly prolonged (Fig 2).

There was a significant increase in the ratio of LVET/PEP in patients with hyperthyroidism ( $4.71 \pm 0.69$  and  $4.42 \pm 0.41$  for Groups 2 and 3 respectively compared to a control of  $3.52 \pm 0.31$   $p < 0.0005$ ). To a smaller degree this occurred in patients with successfully treated hyperthyroidism ( $3.95 \pm 0.63$  Fig 3).

**2 STI in patients with hypothyroidism** In hypothyroid patients (untreated or on treatment Groups 5 and 6) PEP was prolonged significantly ( $159.8 \pm 17.4$  msec and  $149.7 \pm 14.1$  msec respectively) in comparison with the control group ( $p < 0.0005$ ). The LVET was shortened ( $398.4 \pm 14.3$  msec and  $400.1 \pm 14.5$  msec respectively see Figs 1 and 2). The ratio LVET/PEP was therefore significantly decreased in patients with hypothyroidism ( $2.52 \pm 0.15$  and  $2.7 \pm 0.3$  respectively ( $p < 0.0005$ )). Fig 3). Euthyroid patients with previous hypothyroidism did not differ from the controls (Figs 1 to 3).

**3 Correlation between thyroid function tests and STI** A significant linear correlation

( $r = -0.67$   $p < 0.001$ ) between PEP and T (Fig 4) as well as between LVET/PEP and T, ( $r = 0.64$   $p < 0.001$  Fig 5) was found.

The correlation between PEP and FTI ( $r = -0.58$ ) followed an exponential curve. The same was noted with the correlation LVET/PEP and FTI ( $r = 0.58$ ). If plotted in a semilogarithmic way the correlation between these two parameters and FTI improved ( $r = -0.68$   $r = 0.66$  respectively  $p < 0.001$ ) and seems to be linear. The semilogarithmic plotting of the correlation between PEP and FTI is shown in Fig 6.

**4 Serial studies in patients with thyroid dysfunction** In seven patients (three with hypothyroidism and four with hyperthyroidism) serial determinations of both STI and thyroid function tests were done. As shown in Fig 7 abnormal PEP values returned to normal during treatment of thyroid dysfunction in five of seven patients, while the other two showed a tendency to return towards normal. This documents the value of serial determinations of PEP during treatment.

**5 The Achilles reflex time compared with the PEP in the assessment of thyroid dysfunction** In 33 patients 46 measurements of both Achilles

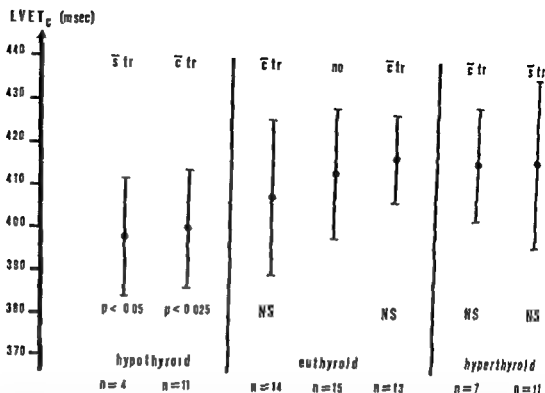


Fig 2 The corrected left ventricular ejection time (LVET<sub>c</sub>) is not significantly altered in hyperthyroidism but shows a tendency to shorten in hypothyroidism. p values represent significance of the patient group compared with the group of normal controls (no). NS = not significant. str = without treatment. etr = on treatment.

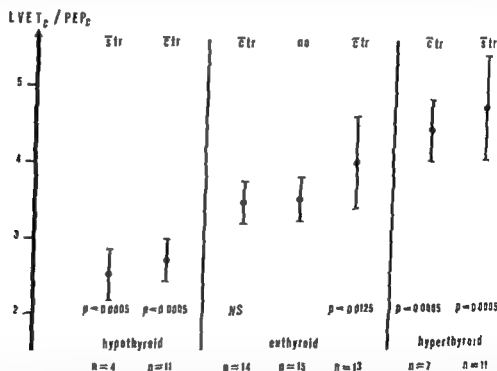


Fig 3 The ratio LVET<sub>c</sub> / PEP<sub>c</sub> reveals a significant shortening in patients with hypothyroidism but is increased in hyperthyroidism. p values represent significance of the patient group compared with the group of normal controls (no). NS = not significant. str = without treatment. etr = on treatment.

reflex time and PEP were performed simultaneously. The determination of PEP permitted a better classification of patients with thyroid dysfunction. This was mainly due to a wide range of Achilles reflex times. Patients with untreated hyperthyroidism revealed no significant change in

Achilles reflex time in comparison with normal controls (Fig 8 Table II).

#### Discussion

In this study of 17 patients with hyperthyroidism (18 determinations) there was a signifi-

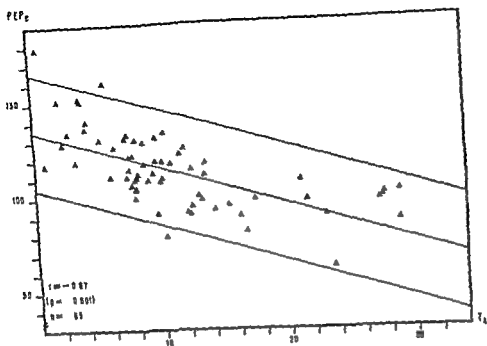


Fig 4 In this figure the correlation between PEP and T is depicted  $n = 65$   $r = -0.67$  ( $p < 0.001$ )

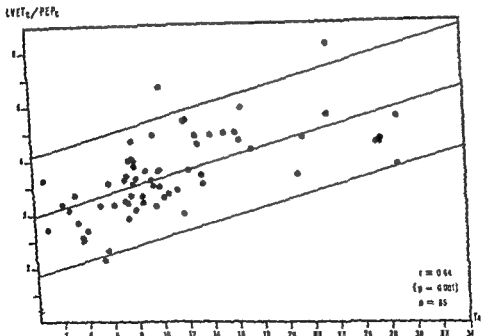


Fig 5 The graph shows the correlation between LVET /PEP and T

cant shortening of PEP documenting an enhanced myocardial contractility caused by thyroid hormones. The LVET was not significantly altered in this group. In eight patients with hypothyroidism (16 determinations) PEP was prolonged due to a decreased myocardial

contractility. The shortening of LVET suggests a fall in stroke volume. These results confirm the findings of other authors who found a shortening of PEP in hyperthyroid patients<sup>21, 23</sup> and a prolongation of PEP as well as a shortening of LVET in hypothyroid patients.<sup>2</sup>

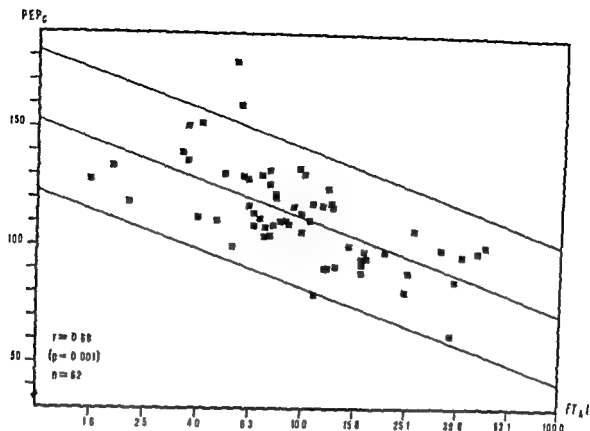


Fig 6 The correlation between PEP and the free T Index (FTI) is linear if the FT values are plotted in a logarithmic way

In all but one of our patients with thyroid dysfunction PEP differed at least 1 SD from the mean of our control values. In 25 patients it differed by 2 SD or more. This means that even if one applies 2 SD (Fig 9), thyroid function can be evaluated correctly in approximately 75 per cent of patients.

Since thyroid function did affect the LVET, less than PEP, the determination of PEP alone was more helpful in assessing thyroid function than the calculation of the ratio LVET/PEP.

The sensitivity of the method is further documented by the change in PEP observed in patients with thyroid dysfunction on treatment (Fig 1).

In two patients with isolated  $T_4$  hyperthyroidism the PEP values were shortened by more than 2 SD below our normal values suggesting the usefulness of PEP in the confirmation or detection of this unusual form of thyrotoxicosis. Hence, we feel that in the case of a normal  $T_4$  and a shortened PEP,  $T_4$  levels should be determined.

Serial measurements of PEP during the treatment of thyroid dysfunction were particularly helpful. Five out of seven patients with abnormal

thyroid function in whom serial determinations of PEP were performed showed a normalization of this time interval after successful treatment. In the other two patients there was a change towards normal (Fig 7).

In our experience the Achilles reflex time is of little help in hyperthyroid patients where PEP is the most valuable parameter. Patients with hypothyroidism may be evaluated by both methods PEP, again being better related to thyroid dysfunction (Fig 8).

The influence of thyroid hormones on the STI is further documented by the correlation between thyroid function and PEP as well as the ratio LVET/PEP. The correlation between  $T_4$  and PEP and  $T_4$  and LVET/PEP seems to be linear (Figs 4 and 5). If the FTI was chosen instead of  $T_4$ , the correlation between these parameters was linear only if plotted in a semilogarithmic way (Fig 6). This correlation may be explained by a maximum enhancement of myocardial contractility in patients with severe hyperthyroidism. These patients show excessive values of the free thyroid hormone not bound to the carrier protein thyroid binding globulin (TBG). The free hormone is the only metabolically active form of

Table II Achilles reflex time compared with PEP in thyroid dysfunction

|         | ASR $\pm$ 1 S.D.<br>(ms c)   | PEP $\pm$ 1 S.D.            |
|---------|------------------------------|-----------------------------|
| Group 1 | 230.4 $\pm$ 45.7<br>(n = 8)  | 119.4 $\pm$ 8.4<br>(n = 8)  |
| Group 2 | 260.8 $\pm$ 85.7<br>(n = 6)  | 84.7 $\pm$ 14.3<br>(n = 6)  |
|         | NS                           | p < 0.0005                  |
| Group 3 | 234.6 $\pm$ 27.9<br>(n = 5)  | 93.2 $\pm$ 9.7<br>(n = 5)   |
|         | p < 0.075                    | p < 0.0005                  |
| Group 4 | 203.5 $\pm$ 35.2<br>(n = 9)  | 108.4 $\pm$ 16.9<br>(n = 9) |
|         | NS                           | NS                          |
| Group 5 | 274.6 $\pm$ 134.9<br>(n = 4) | 160.0 $\pm$ 27.0<br>(n = 4) |
|         | p < 0.01                     | p < 0.0005                  |
| Group 6 | 390.0 $\pm$ 67.8<br>(n = 5)  | 153.4 $\pm$ 16.5<br>(n = 5) |
|         | p < 0.005                    | p < 0.0005                  |
| Group 7 | 290.8 $\pm$ 39.9<br>(n = 9)  | 117.9 $\pm$ 8.8<br>(n = 9)  |
|         | NS                           | NS                          |

The latter is more accurately correlated to the FTI than to the T value which mainly measures the bound fraction

The recent development of new biochemical procedures for investigation of thyroid dysfunction (radioimmunoassays for  $T_3$  and TSH as well as the TRH test) allows the detection of minor degrees of thyroid dysfunction in very early stages (preclinical hyper and hypothyroidism).

In some cases these tests are too sensitive and their clinical significance can be disputed (e.g. elevated levels of TSH or thyroid hormones in euthyroid subjects or hyperthyroidism with normal values for T and FTI).

In the meantime we have seen 12 patients in whom one of the laboratory parameters of thyroid function was abnormal but who had no clinical evidence for thyroid dysfunction. In all of these patients the systolic time intervals were within normal limits. We feel that in such cases the systolic time intervals may be of help in the clinical evaluation of thyroid function.

The usefulness of this noninvasive test is furthermore stressed by advantages such as immediate availability, easy repetition and safety. However in patients with intrinsic heart disease in addition to hypothyroidism PEP

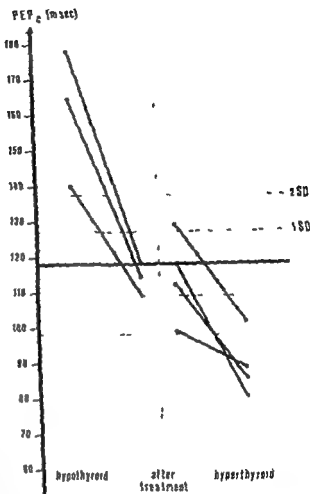
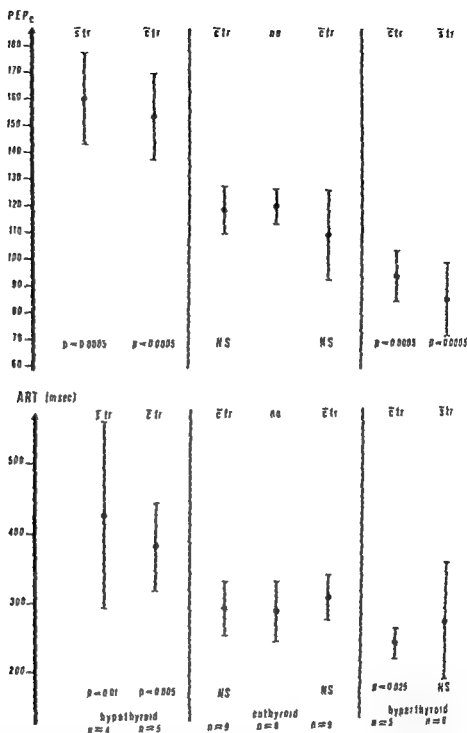


Fig. 7 In five of seven patients with thyroid dysfunction in whom serial studies of PEP were done this time interval returned to the normal range ( $\pm$  1 S.D.) after successful treatment.

would be expected to be prolonged out of proportion for their hypothyroid state alone. A further practical drawback lies in the fact that STI are of no help in patients receiving  $\beta$  blocking agents for hyperthyroidism.

### Summary

The systolic time intervals (LVET, PEP and ratio LVET/PEP) were determined in 53 patients presenting with signs or symptoms of thyroid dysfunction. Patients with clinical evidence for congestive heart failure with arterial hypertension or old myocardial infarction and patients receiving cardioactive drugs were excluded from the study. Thyroid function was evaluated by means of T RIA, serum thyroxine and TRH stimulation test.



**Fig 8** This figure compares the usefulness of PEP and the Achilles tendon reflex time (ART) in the assessment of thyroid dysfunction. The determination of PEP permits a better classification than the ART. Values represent difference between the patient group and the normal controls.

In patients with hyperthyroidism (untreated and on treatment) PEP was shortened significantly ( $91.7 \pm 11.0$  msec compared to a control of  $118 \pm 9.3$  msec). LVET was prolonged only insignificantly. Hence the ratio LVET/PEP<sub>c</sub> showed a significant increase in hyperthyroid patients.

In hypothyroid patients (untreated and on treatment) PEP<sub>c</sub> was prolonged to  $152.4 \pm 15.1$  msec. LVET<sub>c</sub> was shortened ( $399.7 \pm 14.4$  msec

compared to a control of  $413.7 \pm 15.9$  msec). The ratio LVET<sub>c</sub>/PEP<sub>c</sub> was decreased. In seven patients, serial determinations of PEP<sub>c</sub> were performed; the values returned towards normal after successful treatment of thyroid dysfunction.

A significant linear correlation between PEP and T<sub>4</sub> ( $r = -0.67$ ) as well as LVET/PEP<sub>c</sub> and T<sub>4</sub> ( $r = 0.64$ ) was found. In 17 patients with hyperthyroidism and in eight patients with hypo

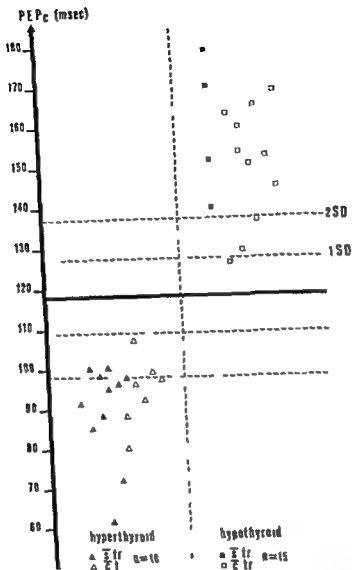


Fig 9 PEP values of 18 patients with hyper and 15 patients with hypothyroidism are shown in this figure. Thirty two of 33 PEP values of these patients with thyroid dysfunction were outside the normal range ( $\pm 1$  SD).

thyroidism 33 determinations of PEP were performed. All but one of the values differed by at least 1 SD from our normal group or taking 2 SD thyroid function could be evaluated correctly in approximately 75 per cent of patients.

We wish to thank J Girard M D for the performance of the TSH assays. Furthermore the authors gratefully acknowledge the helpful comments of Prof G M Besser St Bartholomew's Hospital London.

#### REFERENCES

- 1 Grossman W, Rolin N I, Johnson L, W Brooks H L, Selenkow H A and Dexter L. The enhanced

myocardial contractility of thyrotoxicosis. *Ann Intern Med* 74:869 1971.

- 2 Lüdert B. Herzfunktion bei Hyperthyreose. *Internist* 16:574 1975.
- 3 Pietras R J, Real M A, Potucha H S, Bronsky D and Waldtem S S. Cardiovascular response in hyperthyroidism. *Arch. Intern Med* 129:426 1979.
- 4 Buccino R A, Spann J F, Pool P H, Sonnenblick E H and Braunwald E. Influence of the thyroid state on the intrinsic contractile properties and energy stores of the myocardium. *J Clin Invest* 46:1669 1967.
- 5 Seidinger M, Walser A, Burkart F and Burckhardt D. Cardiac output in thyroid disease. *Experientia* 28:915 1972.
- 6 Howitt J, Rowlands D J, Leung Y T, and Logan W F W E. Myocardial contractility and the effects of



- beta adrenergic blockade in hypothyroidism and hyperthyroidism *Chn Sci* 34 485 1968
- 7 Weissler A M Harris W S and Schoenfeld C D Systolic time intervals in heart failure in man *Circulation* 37 149 1968
  - 8 Ahmed S S Levinson G E Schwartz C J and Ettinger P O Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man *Circulation* 46 559 1972
  - 9 Hoffmann A Seifdpar M and Burckhardt D Systolische Zeitintervalle in Ruhe und unter Belastung bei unterschiedlichem Schweregrad von Linksherzinsuffizienz *Z Kardiologie* 63 768 1974
  - 10 Weissler A M Harris W S and Schoenfeld C D Bedside techniques for the evaluation of ventricular function in man *Am J Cardiol* 23 577 1969
  - 11 Mitsuma T Gershengorn M C Colucci J and Hollander C S Radioimmunoassay of triiodothyronine in unextracted human serum *J Clin Endocrinol* 33 364 1971
  - 12 Hershman J M and Pittman J A Utility of the radioimmunoassay of serum thyrotropin in man *Ann Intern Med* 74 481 1971
  - 13 Hall R Amos J Garry R and Buxton H L Thyroid stimulating hormone response to synthetic thyrotropin releasing hormone in man *Br Med J* 11 274 1970
  - 14 Staub J J Girard J Genssenjager E and Muller J Oral TRH as a simple diagnostic test for thyroid investigation with special regard to patients with low response *Eur J Clin Invest* 6 7 p 1976
  - 15 Murphy B E P and Pattee C J Determination of thyroxine utilizing the property of protein binding *J Clin Endocrinol* 24 187 1964
  - 16 Staub J J TRH test in subacute thyroiditis *Lancet* 1 868 1975
  - 17 Staub J J Barthe P L Werner I and Girard J Early detection of relapse in hyperthyroidism by TRH test *Lancet* 11 661 1975
  - 18 Hennemann G Van Welsum M Bernard B Docter R and Visser T J Serum thyrotropin concentration an invalid test for detection of early hypothyroidism after thyroidectomy *Br Med J* 11 129 1975
  - 19 Britton K E Quinn V Ellis S M Cayley A C D Miralles J M Brown B L and Ekins R P Is "T toxicosis" a normal biochemical finding in elderly women? *Lancet* 11 141 1975
  - 20 Hesch B D and Everett D C Radioimmunoassay of triiodothyronine in unextracted human serum *Br Med J* 1 645 1973
  - 21 Amidi M Leon D F De Groot W J Kroetz F W and Leonard J J Effect of the thyroid state on myocardial contractility and ventricular ejection rate in man *Circulation* 38 229 1968
  - 22 Pansì A F Hamilton B P Thomas, Ch N and Mazzaferri E L The short cardiac pre ejection period An index to thyrotoxicosis *Circulation* 49 900 1974
  - 23 Hallis W S Bremner W F Lawrie T D V and Thomson J A Systolic time intervals in thyroid disease *Clin Endocrinol* 4 617 1975
  - 24 Hershman J M and Pittman J A Jr Response to synthetic thyrotropin releasing hormone in man *J Clin Endocrinol* 31 457 1970
  - 25 Haigler E D Hershman J M and Pittman J A Response to orally administered synthetic thyrotropin releasing hormone in man *J Clin Endocrinol* 35 631 1972
  - 26 Vagenakis A G Rapoport B Azizi F Portnau G I Braverman L F and Ingbar S H Hyperresponse to thyrotropin releasing hormone accompanying small decreases in serum thyroid hormone concentrations *J Clin Invest* 54 913 1974
  - 27 Snyder P J and Utiger R D Inhibition of thyrotropin response to thyrotropin releasing hormone by small quantities of thyroid hormones *J Clin Invest* 51 901 1972
  - 28 Shenkman L Mitsuma T and Hollander C S Modulation of pituitary responsiveness to thyrotropin releasing hormone by triiodothyronine *J Clin Invest* 52 700 1973
  - 29 Gerstner J B and Caplan R H Hyperthyroidism with normal concentrations of total serum thyroxine and triiodothyronine *J Clin Endocrinol* 42 64 1976

## The effects of psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog\*

Regis A DeSilva MB FRCP (C)

Richard L Verner PhD FACC

Bernard Lown MD FACC

Boston Mass

Recent studies have emphasized the importance of neural and psychological factors in the occurrence of sudden death.<sup>1</sup> In the experimental animal diverse psychologic stresses lower the vulnerable period threshold for ventricular fibrillation.<sup>2</sup> In man psychologic stresses have been associated with the occurrence of arrhythmias and the precipitation of sudden death. These stresses are mediated largely through the sympathetic limb of the autonomic nervous system. Enhanced sympathetic neural tone whether resulting from subcortical<sup>3,4</sup> hypothalamic<sup>5</sup> or stellate ganglion stimulation<sup>6</sup> or whether the consequence of catecholamine administration<sup>7</sup> predisposes to ventricular fibrillation. In contrast increased vagus nerve activity whether by electrical or pharmacologic means<sup>8</sup> exerts a protective effect against ventricular fibrillation when sympathetic tone is augmented.

These observations suggest that drugs which alter psychologically initiated neural inputs to the heart will diminish susceptibility to ventricular

ular fibrillation. In modeling such experiments in animals one is confronted by methodologic difficulties. The study of vulnerability in the conscious state using VF as an endpoint is complicated by two considerations. Firstly it is inhumane to subject animals repeatedly to the high currents necessary to provoke VF and the high electrical energies required to terminate this arrhythmia. Secondly resuscitative efforts alter autonomic tone and induce trauma vitiating meaningful investigation of psychologic variables. These methodologic difficulties may be surmounted by utilizing the repetitive extrasystole (RE) as an endpoint rather than VF. Matta and associates<sup>9</sup> have demonstrated that there is concordance between the threshold currents required to elicit VF and RE. About 66 per cent of the current required to induce VF will consistently result in a repetitive response. The nadir of threshold for both VF and RE are coincident in the cardiac cycle. Furthermore during interventions such as electrical stimulation of the vagus and stellate ganglia, catecholamine infusion and beta adrenergic blockade identical shifts occur in these two periods within the cardiac cycle.<sup>10</sup>

In the present study RE threshold was employed to determine the effects of morphine sulfate on cardiac vulnerability in the psychologically stressed animal. This drug is widely used to allay anxiety and pain during the inception of an acute cardiac ischemic episode at a time when there is marked susceptibility to VF. However no information exists on the action of morphine on ventricular vulnerability in the awake animal.

From the Cardiovascular Research Laboratory, Department of Nutrition, Harvard School of Public Health, Boston, Mass.

Supported in part by Grant MH 1384 from the National Institute of Mental Health and by Grant HL 07776 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, United States Public Health Service.

Received for publication May 29, 1977.  
Accepted for publication May 17, 1977.

Reprint requests: Bernard Lown MD, Professor of Cardiology, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, Mass. 02115.

Presented in part at the American College of Cardiology Meeting in Las Vegas, Nevada, March 8, 1977.

The purpose of this study was twofold (1) to investigate the time course of changes in vulnerability associated with psychological stress and (2) to determine if morphine alters the response to stress, and if so, to define the mechanism(s) of its actions

### Material and methods

**Surgical procedures** Twelve healthy adult mongrel dogs of either sex weighing 9.0 to 15.0 kilograms were selected for study. All dogs were tested and were found to be free from heart worms (*Dirofilaria immitis*). Seven days prior to the definitive investigation the animals were anesthetized with intravenous methohexital (10 mg/Kg). A recording catheter (Elecath 003992) and a bipolar pacing catheter (Medtronic 6901, interelectrode distance 28 mm) were positioned in the right ventricle via a jugular vein as previously described.<sup>16, 17</sup> The tip of the pacing catheter was wedged firmly in the apex of the right ventricle. A blood pressure catheter was passed retrograde into the aorta through an omocervical artery and flushed with concentrated heparin. All catheters were exteriorized at the nape of the neck. Mean arterial blood pressure was measured by electrically integrating the pulsatile output of a Statham 23dB pressure transducer.

**Electrical testing of the heart** Ventricular vulnerability to fibrillation was assessed by the repetitive extrasystole (RE) threshold method.<sup>18</sup> A Medtronic battery powered pacemaker provided rectangular 2 msec pulses at 273 msec intervals. This rate (220 beats/minute) was necessary to override tachycardia in the stressful environment and following atropine administration. The distal pole was made cathodal and the pacemaker output was adjusted to twice the mid diastolic threshold. A special purpose constant-current pulse generator with an electrically isolated output provided test stimuli of 5 msec duration. It was equipped with circuitry to inhibit the pacemaker output for 3 seconds immediately following the test stimulus. The vulnerable period threshold was determined as follows: with heart rate maintained at 220 beats/minute scanning for the RE threshold was commenced with a stimulus intensity of twice the mid diastolic threshold starting 30 msec beyond the refractory period. The test stimulus was delivered progressively earlier by 5 msec intervals until the refractory

period was encountered. If no RE resulted the stimulus intensity was increased by 2 ma and the scanning procedure was repeated. The RE threshold was taken to be the minimum current intensity at which RE occurred in two out of three trials. This method provided a more rapid assessment of the vulnerable period threshold than sequential R/T pulsing utilized in previous studies.<sup>18</sup>

Ventricular fibrillation was rare with this method. When it occurred, defibrillation was accomplished within 60 seconds. The study was then discontinued and the animal was tested the following day.

**Psychologic environments** The animals were studied in two environments as previously described.<sup>19</sup> The nonstressful environment consisted of a large cage in a sound attenuated room. A counterbalanced cable suspended from the top of the cage contained connections for the cardiac and blood pressure catheters. This permitted the animal to move freely within the cage. The animals appeared relaxed and after a few minutes were lying down quietly.

The stressful environment consisted of a Pavlovian sling in which the animal was restrained and movement was limited. Cables were connected to the cardiac catheters so that a continuous oscilloscopic display of the ECG was obtained and pacing and test stimuli could be delivered. A single 5 msec shock from a cardioverter was delivered via copper plates (80 cm<sup>2</sup>) fastened across the thorax. The dog remained in the sling for 10 minutes before the synchronized transthoracic shock was administered and for 10 minutes following the shock.

**Experimental protocol** The psychological conditioning protocol was as follows: six dogs were exposed first to the sling environment and then to the cage setting. In the remaining six dogs the sequence was reversed.

All animals were exposed to both environments on three consecutive days prior to cardiac testing. A 5 msec transthoracic shock was administered in the sling on each of these days. No further shocks were administered after the third day. This conditioning period was selected based on earlier experiments which showed that maximal effects on RE threshold are evident after this period.<sup>4</sup> Measurement of heart rate, arterial blood pressure and RE threshold was commenced on the fourth day. These determinations were carried out after the

Table I Summary of experimental protocol

| Day | Experimental procedure   |
|-----|--|
| 1-3 | Aversive conditioning in sling followed by placement in cage. Placement in cage followed by aversive conditioning in sling |
| 4   | Electrical testing for RE threshold in cage and sling environments   |
| 5   | Administration of MS in sling environment. Administration of atropine following MS (6 dogs)                                |
| 6   | Non study day to allow dissipation of morphine   |
| 7   | Electrical testing for RE threshold in cage and sling environments. Administration of MS in cage environment               |
| 8   | Study of time-course of recovery in RE threshold in cage   |

animal had been in the cage environment for one hour and when in the sling for 10 minutes. The six dogs in the sling to cage paradigm were studied again on the eighth day. In these dogs RE threshold, heart rate and blood pressure measurements were made at 10 minutes in the sling. Additional measurements were made at 10, 30, 50 and 70 minutes in the cage. Morphine sulfate (0.25 mg/kg) was injected intravenously on the fifth day of study 30 minutes before placing the dogs in the sling environment. After determining the effect of MS on heart rate, arterial blood pressure and repetitive extrasystole threshold, atropine sulfate (0.2 mg/kg intravenously) was given to six dogs. Threshold determinations were made within 15 minutes after administration of atropine. One day was allowed for drug dissipation and on the seventh day repetitive extrasystole thresholds were redetermined to assess the presence of the effect of aversive conditioning. In the six dogs which had been exposed to the sling to cage paradigm, morphine sulfate (0.25 mg/kg) was given in the cage setting to determine the influence of the drug in the absence of aversive stimuli. A summary of the protocol is shown in Table I.

Results were analyzed using Student's *t* test for paired data. The criterion of significance was  $P < 0.05$ .

#### Results

**Influence of psychological environment on ventricular vulnerability.** The animals exhibited different behavioral responses after three days of conditioning in the two environments. The dogs

Table II Effect of repetitive extrasystole (RE) threshold in dogs placed first in a nonaversive cage setting followed by an aversive sling environment. The influence of morphine sulfate (MS) (0.25 mg/kg) was determined on day 5.  $N = 11$  dogs

| Day of study | RE threshold (ma)    |                | P         |
|--------------|----------------------|----------------|-----------|
|              | Cage                 | Sling          |           |
| 4            | $37 \pm 5^{\dagger}$ | $18 \pm 2$     | $< 0.01$  |
| 5            | $28 \pm 4$           | (MS) $1 \pm 2$ | $< 0.01$  |
| "            | $27 \pm 3$           | $20 \pm 2$     | $< 0.01$  |
|              | NS                   | P              | $< 0.001$ |

†Values are means  $\pm$  SEM

Ref vs to statistical comparisons between sling and cage

Ref vs to statistical comparisons between MS-treated and control animals

Table III Effect on RE threshold of placing dogs first in sling and then in cage.  $N = 6$  dogs

| Day of study | RE threshold (ma)    |                 | P        |
|--------------|----------------------|-----------------|----------|
|              | Sling                | Cage            |          |
| 4            | $17 \pm 4^{\dagger}$ | $31 \pm 5$      | $< 0.01$ |
| 5            | (MS) $7 \pm 4$       | — <sup>††</sup> | —        |
| 6            | $13 \pm 4$           | $23 \pm 4$      | $< 0.01$ |
|              | P                    | NS              |          |

Refers to statistical comparisons between sling and cage

Refers to statistical comparisons between MS-treated and control animals

†Values not obtained due to prior administration of MS in sling environment

††Values are means  $\pm$  SEM

entered the nonstressful cage voluntarily and usually lay down within a few minutes. In contrast, entry into the sling environment was resisted. In the sling, animals exhibited increased muscular tone, somatic tremor and occasionally there was loss of sphincter control. Heart rate increased from  $102 \pm 5$  to  $134 \pm 3$  beats/minute ( $P < 0.01$ ) and arterial blood pressure rose from  $84 \pm 6$  to  $120 \pm 5$  mm Hg ( $P < 0.01$ ). The RE threshold for all 12 dogs was 45 per cent lower in the sling as compared to the cage ( $P < 0.01$ ) (Tables II and III). The sequence with which the animals were placed in the two settings did not appear to affect the changes in the above determinations.

**Time course of changes in ventricular vulnerability.** In six animals, significant reduction in RE threshold and increase in heart rate and blood pressure occurred within 10 minutes after being

The purpose of this study was twofold (1) to investigate the time course of changes in vulnerability associated with psychological stress and (2) to determine if morphine alters the response to stress, and if so to define the mechanism(s) of its actions

### Material and methods

**Surgical procedures** Twelve healthy adult mongrel dogs of either sex weighing 9.0 to 15.0 kilograms were selected for study. All dogs were tested and were found to be free from heart worms (*Dirofilaria immitis*). Seven days prior to the definitive investigation the animals were anesthetized with intravenous methohexital (10 mg/Kg). A recording catheter (Elecath 003992) and a bipolar pacing catheter (Medtronic 6901 interelectrode distance 28 mm) were positioned in the right ventricle via a jugular vein as previously described.<sup>16, 17</sup> The tip of the pacing catheter was wedged firmly in the apex of the right ventricle. A blood pressure catheter was passed retrograde into the aorta through an omocervical artery and flushed with concentrated heparin. All catheters were exteriorized at the nape of the neck. Mean arterial blood pressure was measured by electrically integrating the pulsatile output of a Statham 23dB pressure transducer.

**Electrical testing of the heart** Ventricular vulnerability to fibrillation was assessed by the repetitive extrasystole (RE) threshold method.<sup>18</sup> A Medtronic battery powered pacemaker provided rectangular 2 msec pulses at 273 msec intervals. This rate (220 beats/minute) was necessary to override tachycardia in the stressful environment and following atropine administration. The distal pole was made cathodal and the pacemaker output was adjusted to twice the mid diastolic threshold. A special purpose constant-current pulse generator with an electrically isolated output provided test stimuli of 5 msec duration. It was equipped with circuitry to inhibit the pacemaker output for 3 seconds immediately following the test stimulus. The vulnerable period threshold was determined as follows: with heart rate maintained at 220 beats/minute scanning for the RE threshold was commenced with a stimulus intensity of twice the mid diastolic threshold starting 30 msec beyond the refractory period. The test stimulus was delivered progressively earlier by 5 msec intervals until the refractory

period was encountered. If no RE resulted, the stimulus intensity was increased by 2 ma and the scanning procedure was repeated. The RE threshold was taken to be the minimum current intensity at which RE occurred in two out of three trials. This method provided a more rapid assessment of the vulnerable period threshold than sequential R/T pulsing utilized in previous studies.<sup>19</sup>

Ventricular fibrillation was rare with this method. When it occurred defibrillation was accomplished within 60 seconds. The study was then discontinued and the animal was tested the following day.

**Psychologic environments** The animals were studied in two environments as previously described.<sup>20</sup> The nonstressful environment consisted of a large cage in a sound attenuated room. A counterbalanced cable suspended from the top of the cage contained connections for the cardiac and blood pressure catheters. This permitted the animal to move freely within the cage. The animals appeared relaxed and after a few minutes were lying down quietly.

The stressful environment consisted of a Pavlovian sling in which the animal was restrained and movement was limited. Cables were connected to the cardiac catheters so that a continuous oscillographic display of the ECG was obtained and pacing and test stimuli could be delivered. A single 5 wsec shock from a cardioverter was delivered via copper plates (80 cm<sup>2</sup>) fastened across the thorax. The dog remained in the sling for 10 minutes before the synchronized transthoracic shock was administered and for 10 minutes following the shock.

**Experimental protocol** The psychological conditioning protocol was as follows: six dogs were exposed first to the sling environment and then to the cage setting. In the remaining six dogs the sequence was reversed.

All animals were exposed to both environments on three consecutive days prior to cardiac testing. A 5 wsec transthoracic shock was administered in the sling on each of these days. No further shocks were administered after the third day. This conditioning period was selected based on earlier experiments which showed that maximal effects on RE threshold are evident after this period.<sup>21</sup> Measurement of heart rate, arterial blood pressure and RE threshold was commenced on the fourth day. These determinations were carried out after the

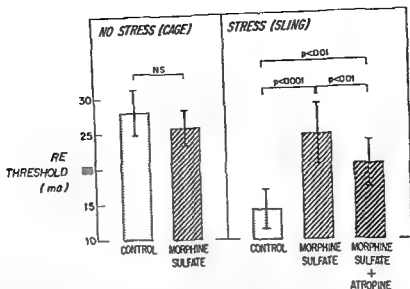


Fig 3 Effect of morphine sulfate (MS) on RE threshold in the two environments. Morphine (0.5 mg/kg) significantly elevated RE threshold in the sling environment by 40 per cent ( $p < 0.001$ ). Administration of atropine sulfate (0.2 mg/kg) following MS partially annulled this effect but RE threshold still remained significantly above the control level in the sling ( $p < 0.01$ ). MS was without effect on RE threshold in the cage environment.

was  $81 \pm 4$  mm Hg in the control state and  $87 \pm 7$  mm Hg following morphine.

### Discussion

The cardiovascular response to psychological stress is a complex composite of several adaptive processes representing an integrated pattern of interactions between the higher cortical centers, hypothalamus and medullary vasomotor centers. Perception of a stressful environment results in neural and humoral changes provoking alterations in autonomic function with catecholamine and adrenocortical hormone release. This cortico-hypothalamic reaction is reflected in somatomotor alterations manifest in part by an increase in blood pressure, marked inotropic and chronotropic effects on the heart, and increase in muscle tone.<sup>1</sup> The cardiovascular response to stress involves both vagal inhibition and sympathetic stimulation.<sup>1</sup> To date the focus of study of the cardiovascular response to higher neural and psychologic inputs has involved hemodynamic effects. Little attention has been given to heart rhythm alterations. That substantial changes may be elicited is indicated by recent findings that stimulation of the posterior hypothalamus results in a 40 per cent reduction in VF threshold. In animals with acute myocardial ischemia

electric stimuli to the hypothalamus induce ventricular fibrillation. In the conscious state psychological stress reduces the vulnerable period threshold by 50 per cent.<sup>1</sup>

In the present study restraining the animals in an aversive environment consistently evoked marked increases in ventricular vulnerability in heart rate and in blood pressure. This response to stress was not extinguished for five days after cessation of the painful stimulus. In the cage to sling paradigm a 45 per cent reduction in the vulnerable period threshold occurred within ten minutes of placement in the stressful environment. This observation demonstrates that psychological stress can alter cardiac vulnerability rapidly and profoundly. Reversing the cage-sling sequence did not alter the magnitude of change in vulnerability. Shifting animals from the aversive sling to the tranquil cage environment permitted determination of the temporal sequence in RE threshold recovery occurring with relaxation. The immediate response was a slowing in heart rate and a decrease in blood pressure. These changes were significant and suggest a lessening of sympathetic activity on the heart and vasculature. However, it is noteworthy that these initial alterations were not accompanied by recovery in vulnerability. There was a striking lag in recovery

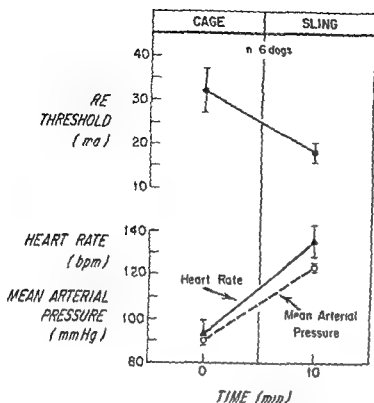


Fig 1 Effect of aversive sling environment on repetitive extrasystolic (RE) threshold heart rate (HR) and arterial blood pressure (BP) in six dogs. The RE threshold decreased 40 per cent within 10 minutes of placing the animals in the sling after removal from the cage. This reduction in threshold was accompanied by significant elevations in heart rate and BP. Values are means  $\pm$  SEM.

moved from cage to sling (Fig 1). The six animals which were shifted from sling to cage exhibited no significant change in RE threshold ( $22 \pm 2$  ma vs  $21 \pm 2$  ma) during the first 10 minutes after transfer. A significant rise in RE threshold occurred after 20 more minutes. Heart rate was  $134 \pm 8$  beats/minute and blood pressure was  $117 \pm 5$  mm Hg in the sling. Upon transfer to the cage, significant reduction in heart rate and blood pressure occurred within the first 10 minutes ( $P < 0.03$ ). No significant changes in RE threshold, heart rate and blood pressure occurred in the last 20 minutes in the cage (Fig 2).

**Effect of MS on RE threshold in the stressful environment.** Administration of MS  $25$  mg/Kg 30 minutes before placing 12 animals in the sling raised RE threshold by 40 per cent ( $P < 0.01$ ). However, RE threshold in this environment even following MS was still significantly lower than that obtained prior to exposing the animals to stress ( $P < 0.01$ ). Heart rate was significantly lowered by morphine from  $135 \pm 3$  to  $104 \pm 3$

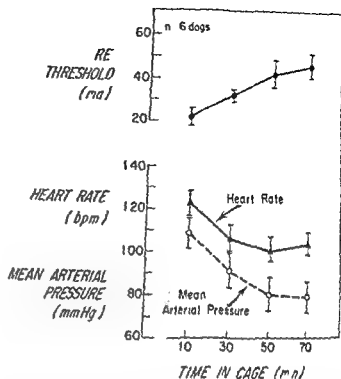


Fig 2 Effect of nonaversive cage environment on RE threshold, heart rate and arterial blood pressure in six dogs. Transferring the animals from the sling to the cage environment resulted in an increase in RE threshold which was evident after 20 minutes. The threshold continued to rise 40 minutes thereafter. In contrast, the changes in heart rate and arterial blood pressure were evident as soon as the animals were placed in the cage; heart rate and arterial blood pressure continued to decrease over the ensuing 40 minutes.

beats/minute ( $P < 0.01$ ) and this rate was similar to that obtained in the non-aversive environment. Blood pressure, however, was unchanged by treatment with morphine. Mean arterial blood pressure was  $119 \pm 4$  mm Hg before and  $115 \pm 5$  mm Hg after morphine administration. Atropine  $0.2$  mg/Kg was administered to six dogs after they had received morphine. In these animals RE threshold in the sling was  $15 \pm 3$  ma and rose after morphine to  $25 \pm 4$  ma ( $P < 0.001$ ) but after atropine receded to  $20 \pm 3$  ma ( $P < 0.01$ ). Following atropine, RE threshold still remained significantly above that obtained before morphine administration ( $P < 0.01$ ) (Fig 3).

**Effect of MS on RE threshold in the non-stressful environment.** No significant change in RE threshold occurred when morphine was administered to animals while in the cage ( $28 \pm 4$  ma vs  $26 \pm 3$  ma after morphine) (Fig 3). Heart rate, however, decreased from  $113 \pm 8$  to  $100 \pm 11$  beats/minute ( $P < 0.02$ ) while pressure remained unaffected. Mean arterial blood pressure

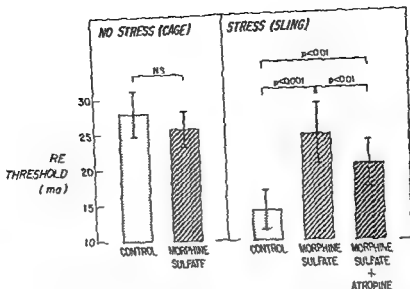


Fig 3 Effect of morphine sulfate (MS) on RE threshold in the two environments. Morphine (0.25 mg/Kg) significantly elevated RE threshold in the sling environment by 40 per cent ( $p < 0.001$ ). Administration of atropine sulfate (0.2 mg/Kg) following MS partially annulled this effect but RE threshold still remained significantly above the control level in the sling ( $p < 0.001$ ). MS was without effect on RE threshold in the cage environment.

was  $81 \pm 4$  mm Hg in the control state and  $87 \pm 7$  mm Hg following morphine.

### Discussion

The cardiovascular response to psychological stress is a complex composite of several adaptive processes representing an integrated pattern of interactions between the higher cortical centers, hypothalamus and medullary vasomotor centers. Perception of a stressful environment results in neural and humoral changes provoking alterations in autonomic function with catecholamine and adrenocortical hormone release.<sup>1,2</sup> This cortico-hypothalamic reaction is reflected in somatomotor alterations manifest in part by an increase in blood pressure, marked inotropic and chronotropic effects on the heart and increase in muscle tone.<sup>3</sup> The cardiovascular response to stress involves both vagal inhibition and sympathetic stimulation.<sup>4</sup> To date the focus of study of the cardiovascular response to higher neural and psychologic inputs has involved hemodynamic effects. Little attention has been given to heart rhythm alterations. That substantial changes may be elicited is indicated by recent findings that stimulation of the posterior hypothalamus results in a 40 per cent reduction in VF threshold. In animals with acute myocardial ischemia

electric stimuli to the hypothalamus induce ventricular fibrillation. In the conscious state psychological stress reduces the vulnerable period threshold by 50 per cent.<sup>5,10</sup>

In the present study restraining the animals in an aversive environment consistently evoked marked increases in ventricular vulnerability, in heart rate and in blood pressure. This response to stress was not extinguished for five days after cessation of the painful stimulus. In the cage to sling paradigm a 45 per cent reduction in the vulnerable period threshold occurred within ten minutes of placement in the stressful environment. This observation demonstrates that psychologic stress can alter cardiac vulnerability rapidly and profoundly. Reversing the cage-sling sequence did not alter the magnitude of change in vulnerability. Shifting animals from the aversive sling to the tranquil cage environment permitted determination of the temporal sequence in RE threshold recovery occurring with relaxation. The immediate response was a slowing in heart rate and a decrease in blood pressure. These changes were significant and suggest a lessening of sympathetic activity on the heart and vasculature. However, it is noteworthy that these initial alterations were not accompanied by recovery in vulnerability. There was a striking lag in recovery



of RE threshold toward control values which occurred in the ensuing hour associated with further decreases in heart rate and blood pressure. Pretreatment with morphine altered the response to stress. The increase in vulnerability was blunted by 50 per cent. Under the conditions of the present experiment, the protection afforded by morphine against stress induced changes in vulnerability was less than that obtained by returning the animal to a nonstressful environment.

In anesthetized dogs we have demonstrated that the vagotonic action of morphine decreases vulnerability to ventricular fibrillation.<sup>6</sup> Vagal action on vulnerability is indirect and results from a muscarinic inhibition of sympathetic activity.<sup>16</sup> This vagal effect is predetermined by the prevailing level of sympathetic tone. When sympathetic tone is high, cholinergic stimulation results in a substantial elevation of the vulnerable period threshold. Conversely, when adrenergic activity is low or abolished by beta adrenergic blockade, vagal stimulation is attended by insignificant changes in vulnerability.<sup>17</sup> In the present study, sympathetic stimulation was engendered by the stressful environment and the vagotonic action of morphine therefore raised the vulnerable period threshold. Morphine had no effect on vulnerability in the absence of stress as no alterations on the vulnerable period threshold occurred in the nonaversive environment. Vagal activation alone did not account entirely for the action of morphine on vulnerability in the conscious state. Following cholinergic blockade with atropine, the vulnerable period threshold remained significantly elevated above the pre-morphine level. This component of morphine action may be attributed either to a direct effect on the heart or to a central action resulting in sedation and decreased sympathetic outflow. A direct cardiac effect is unlikely as cholinergic blockade in the anesthetized state completely abolishes the effect of morphine on vulnerability. Furthermore, in the tranquil cage environment, morphine was without effect. These observations suggest a central action of morphine which operates significantly only in the presence of stress.

Treatment with morphine induced disparate effects on heart rate and blood pressure. Tachycardia was abolished in the stressful environment while blood pressure was unaffected. Heart rate in the nonstressful environment was significantly

reduced but blood pressure again remained unchanged. The effect on heart rate may be accounted for by an indirect vagotonic action<sup>18</sup> as well as by a direct action of morphine on slowing the sinoatrial node.<sup>24</sup> The effect on vulnerability was not secondary to slowing of heart rate as vulnerable period thresholds were measured at a paced rate of 220 beats/minute. Increase in blood pressure during stress results largely from central sympathetic discharge resulting in vasoconstriction and increases in heart rate and myocardial contractility.<sup>25</sup> Alam and Smirk<sup>9</sup> have called attention to receptors in skeletal muscle which respond to strong and sustained contraction of small muscle groups. Activation of these receptors excites the vasomotor centers and this results in further sympathetic outflow. Morphine would tend to antagonize these effects as it causes vasodilation by the release of histamine from smooth muscle.<sup>26</sup> However, neither this effect nor the sedative and vagotonic actions of the drug were adequate in abolishing the adrenergic pressor response completely.

### Summary

Ventricular vulnerability to fibrillation was assessed in 12 conscious dogs in aversive and nonaversive environments using the repetitive extrasystole (RE) threshold method. In the aversive environment, RE threshold was 45 per cent lower than in the nonaversive setting and heart rate and blood pressure were significantly elevated. This decrease in RE threshold occurred within 10 minutes of exposing the animals to stress. In contrast, the recovery in RE threshold in the nonaversive setting occurred over a 40 minute period. When morphine sulfate (MS) 0.25 mg/Kg was administered to dogs in the aversive environment, the RE threshold was significantly increased. Cholinergic blockade of vagal efferent activity with atropine (0.2 mg/kg) annulled partially the effect of MS on RE threshold. MS was without effect in the nonaversive environment. It is concluded that MS exerts a significant protective effect on increased ventricular vulnerability associated with psychological stress. This effect is mediated by the vagotonic and sedative actions of morphine.

We wish to acknowledge the capable technical assistance of Messrs. Edward Burke, George LeBrun, and Nate Stepper. The authors also thank Ms. Claudia Horen for preparation of the manuscript and Mr. Larry Shearon of Medtronic Inc. of Minneapolis for supplying pacing catheters.

## REFERENCES

- 1 Wolf S Psychosocial forces in myocardial infarction and sudden death, *Circulation* 39 (Suppl IV) 74 1969
- 2 Parkes C M Benjamin B and Fitzgerald R G Broken heart A statistical study of increased mortality among widowers *Br Med J* 1 740 1969
- 3 Engel G L Sudden and rapid death during psychological stress *Ann Intern Med* 74 771 1971
- 4 Johansson G Jonsson L Lannek N Blomgren L Lindberg P., and Poupa O Severe stress-cardiopathy in pigs *Am HEART J* 87 461 1974
- 5 Lown B Temte J V Reich P Gaughan C Regestein R and Hal H The basis for recurring ventricular fibrillation (VF) in the absence of coronary heart disease and its management *N Engl J Med* 294 673 1976
- 6 Lown B and Verner R L Neural activity and ventricular fibrillation *N Engl J Med* 294 1165 1976
- 7 Lown B New concepts and approaches to sudden cardiac death *Schweiz Med Wochenschr* 105 15 2 1976
- 8 Lown B Verner R and Corbalean R Psychological stress and threshold for repetitive ventricular response *Science* 182 834 1973
- 9 Corbalean R Verner R L and Lown B Psychological stress and ventricular vulnerability in the conscious dog *Am J Cardiol* 34 697 1974
- 10 Matta R J Lawler J E and Lown B Ventricular electrical instability in the conscious dog The effects of psychological stress and beta adrenergic blockade *Am J Cardiol* 38 594 1976
- 11 Korteweg E C J Boelen T F and Tencate J Influence of stimulation of some subcortical areas on the electrocardiogram *J Neurophysiol* 20 100 1957
- 12 Hockman C H Mauck H P Jr and Hoff E C ECG changes resulting from cerebral stimulation II A spectrum of ventricular arrhythmias of sympathetic origin *Am HEART J* 71 682 1960
- 13 Manning J W and De V Coiten M Mechanism of cardiac arrhythmias induced by diencephalic stimulation *Am J Physiol* 203 1170 1962
- 14 Verner R L Calvert A and Lown B Effect of posterior hypothalamic stimulation on ventricular fibrillation threshold *Am J Physiol* 228 973 1975
- 15 Verner R L Thompson E G and Lown B Ventricular vulnerability during sympathetic stimulation Role of heart rate and blood pressure *Cardiovasc Res* 8 60 1974
- 16 Rabinowitz S H Verner R L and Lown B The effects of vagosympathetic stimulation on the repetitive extrasystole (RF) threshold *Circulation* 53 672, 1976
- 17 Holman H S Verner R L and Lown B The effect of vagus nerve stimulation upon vulnerability of the canine ventricle Role of sympathetic-parasympathetic interactions *Circulation* 52 518 1975
- 18 Matta R J Verner R L and Lown B The repetitive extrasystole as an index of vulnerability to ventricular fibrillation in the dog *Am J Physiol* 230 1469 1976
- 19 Hilton M M Hypothalamic regulation of the cardiovascular system *Br Med Bull* 22 242 1966
- 20 Hilton S M Ways of viewing the central nervous system—old and new *Brain Res* 87 213 1975
- 21 Selye H The concept of stress in experimental physiology in Tanner J M and Blackwell editors *Stress and psychiatric disorders Oxford 1960 Scientific Publications* p 67
- 22 Ganong W F Gold N J and Hume D M Effect of hypothalamic lesions on plasma 17-hydroxycorticoid response to immobilization in the dog *Fed. Proc* 14 54 1955
- 23 Obrist P A Lawler J E Sutterer J R Smithson K and Martin P L Alterations in cardiac contractility during classical aversive conditioning in dogs. Methodological and theoretical implications *Psychophysiology* 8 246 1971
- 24 Obrist P A Lawler J E Howard J L Smithson K W Martin P L and Manning J Sympathetic influences on cardiac rate and contractility during acute stress in humans *Psychophysiology* 11 406 1974
- 25 Pinotti O Cardiovascular responses to excitement in dogs in Bartorelli C and Zanchetti A editors *Cardiovascular regulation in health and disease Milan 1970 Instituto de Ricerche Cardiovascolari* p 44
- 26 DeSilva R A Verner R L and Lown B Effect of morphine sulfate on vulnerability of the canine ventricle *Clin Res* 24 714A 1976
- 27 Eyster J A E and Meek W J Cardiac irregularities in morphine poisoning in the dog *Heart* 4 59 1919
- 28 Urthaler F Lobe J H Gilmour E K and James T N Morphine and autonomic control of the sinus node *Chest* 64 703 1973
- 29 Alam W and Smirk F H Observations in man on a pulse accelerating reflex from voluntary muscles of the leg *J Physiol (Lond)* 92 187 1938
- 30 Eickenhoff J E and Dech S R The effects of narcotics and antagonists upon respiration and circulation in man *Clin Pharmacol Ther* 1 483 1960

# Post-extrasystolic potentiation of ischemic myocardium by atrial stimulation

George A Diamond MD  
James S Forrester MD  
Protasio L deLuz, MD  
H L Wyatt PhD  
H J C Swan MD, PhD  
Los Angeles Calif

Reports of sometimes dramatic improvement in segmental left ventricular function following coronary bypass surgery although not universal<sup>1-11</sup> leaves the clear implication that ischemic non infarcted myocardium can exist in a state of function hibernation. Afterload reducing agents<sup>1-10</sup> and ventricular post extrasystolic potentiation<sup>11-19</sup> are capable of improving segment dysfunction in man to a degree similar to that observed in the experimental animal.<sup>20-21</sup> Since clinical studies suggest that the response to such agents is predictive of the surgical result the procedure of intervention ventriculography<sup>16</sup> has become widely employed during cardiac catheterization. Post extrasystolic potentiation (PESP) should be the preferred stimulus in this regard since its effect is detectable during the performance of a single ventriculogram but induced ventricular extrasystoles can provoke serious sustained arrhythmias. Premature atrial contractions also elicit the phenomenon of PESP<sup>22</sup> and are inherently safer but no data is available concerning the effects of this stimulus on regional ischemic dysfunction. The present study was undertaken therefore to determine if atrial induced PESP can be used to elicit latent contractile responsiveness in acutely ischemic

myocardium and to define the magnitude and duration of such responsiveness.

## Methods

Studies were carried out in 11 healthy mongrel dogs weighing from 22 to 28 kilograms anesthetized with morphine sulfate (2.2 mg/kg, intramuscular) and chloralose (100 mg/Kg, intravenous). After endotracheal intubation respiration was maintained with a Harvard ventilator. A left thoracotomy was performed via the fifth inter space and the heart was suspended in a pericardial cradle. The distal portion of the left anterior descending coronary artery was isolated for subsequent occlusion. A 6 cm, No 10 French stiff walled Teflon catheter was inserted through the cardiac apex and secured by a purse string suture. This catheter was connected via a three way stopcock directly to a BioTech transducer. The frequency response of this system was determined *in vitro* by calculation<sup>23</sup> from the overshoot of a square wave imposed by gas flame rupture of an air filled balloon attached to the catheter tip. The frequency response was 0 to 45 Hz ( $\pm 10$  per cent). A 100 cm No 7 French polyethylene catheter was inserted into the thoracic aorta via the left femoral artery and attached to a Statham P23DB transducer. The frequency response of this system determined as above was 0 to 20 Hz ( $\pm 10$  per cent). A time delay of 50 msec was present in this system and was corrected by reference to the left ventricular tracing. Pacing electrodes were applied to the right atrium via alligator clips and attached to an external fixed rate synchronous Medtronic stimulator. Left ventricular and aortic pressure were moni-

From the Department of Cardiology Cedars Sinai Medical Center and the Department of Medicine University of California at Los Angeles

With partial support from the National Institutes of Health Grant No HL 15834

Received for publication May 9 1977

Accepted for publication Aug 1 1977

Reprint requests: Publication Office Department of Cardiology Cedars-Sinai Medical Center 8700 Beverly Blvd Los Angeles Calif 90048

0002-8703/78/0295-0204\$00.60/0 © 1978 The C V

tored along with Lead II of the electrocardiogram on a Honeywell multi channel ultraviolet light recorder. As in previous studies from this laboratory<sup>7, 8</sup> a 10 mm mercury in silastic length gauge (0.31 mm inner diameter 0.62 mm outer diameter)\* prestressed for 30 minutes before each experiment was then sutured to the epicardial surface of the left ventricle parallel to the fibers perfused by the left anterior descending coronary artery. The frequency response of this gauge determined via a mechanical oscillator is 0 to 15 Hz ( $\pm 10$  per cent). The time delay is independent of frequency but varies from gauge to gauge (range 0 to 22 msec; mean 15 msec). The stiffness of the gauge is 1 gr force/5 per cent elongation. The length gauge was calibrated prior to use by attaching its ends to the jaws of a vernier caliper and extending the gauge by fixed increments. When in use the arc of epicardium subtended by the gauge varied from 10 to 20 mm. Within such a range the calibration of the gauge is not affected by variations of body temperature and is linear ( $\pm 5$  per cent) for up to 8 hours.

Pre extrasystolic and post extrasystolic end diastolic segment length and the magnitude of diastolic shortening were measured directly from the calibrated length gauge tracing on three consecutive beats. The end diastolic point was defined as the Z point of the left ventricular pressure. Systolic shortening was measured as the difference between length at initial peak left ventricular pressure and length at the aortic diastolic notch (corrected for time delay). All data were collected with the respirator turned off for 5 seconds at end expiration. No drift in baseline was noted with this procedure and cyclic respiratory changes were abolished.

After an initial stabilization period control data were obtained before and following interruption of normal sinus rhythm with a single synchronized atrial paced premature stimulus. The mean interstimulus (R-R) interval between the control and paced beat was  $375 \pm 7$  (1 SD) msec at a mean heart rate of  $102 \pm 10$  (1 SD) and could not be more precisely controlled due to variations in the paced PR interval. The ratio of the post extrasystolic interval to the pre extrasystolic interval was  $1.6 \pm 0.1$  (1 SD). This coupling interval produced potentiation of systolic shortening on the post extrasystolic beat that

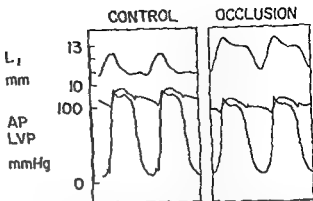


Fig 1 Effect of coronary occlusion on regional function. Note the marked reduction in systolic shortening following occlusion. L = length gauge. LVP = left ventricular pressure. AP = aortic pressure.

was reproducible within 5 per cent on duplicate determination and corresponds to that used in previous studies.<sup>11</sup> In two additional control dogs the degree of augmentation of systolic shortening remained within  $\pm 10$  per cent of control for a period of 5 hours. The left anterior descending coronary artery was then ligated. Data were obtained at 1 and 30 minutes following occlusion in each dog. In nine dogs serial determinations were made each 30 minutes for up to 3 hours post occlusion. Analysis of data for statistical significance was by the paired t test.

## Results

Typical control data before and after coronary occlusion is illustrated in Fig 1. Prior to coronary occlusion regional systolic shortening was  $1.30 \pm 0.29$  mm and increased to  $2.77 \pm 0.42$  mm on the post extrasystolic beat ( $p < 0.001$ ). Following one minute of occlusion systolic shortening had decreased to  $-0.24 \pm 0.06$  mm ( $p < 0.0001$ ) and in eight cases paradoxical systolic lengthening was noted but PESP improved systolic shortening in all dogs to  $1.42 \pm 0.24$  mm ( $p < 0.0001$ ). Thirty minutes following occlusion systolic shortening had spontaneously improved slightly to  $0.32 \pm 0.05$  mm ( $p < 0.001$ ) and increased to  $1.14 \pm 0.23$  mm ( $p < 0.001$ ) following PESP (Figs 2 and 3). Hemodynamic response at 30 minutes was typical of the total experiment. Post extrasystolic left ventricular systolic pressure increased by 22 per cent from  $102 \pm 9$  to  $124 \pm 15$  mm Hg ( $p < 0.001$ ) compared to the pre extrasystolic beat and aortic diastolic pressure decreased 23 per cent from  $76 \pm 6$  to  $59 \pm 5$

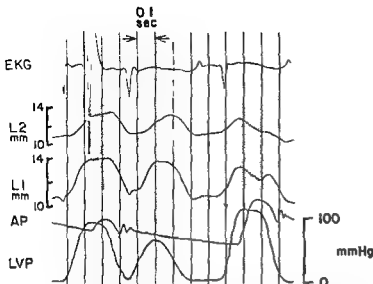


Fig 2 Early responsiveness of ischemic myocardium to post extrasystolic potentiation L represents the length gauge in the central area of ischemia and L<sub>1</sub> a gauge in an adjacent area (not monitored in other experiments) The first beat represents resting (pre extrasystolic) function 30 minutes following left anterior descending coronary artery occlusion. Absence of systolic shortening and slight systolic paradox is evident on both gauges (shaded area) The second beat represents the extrasystolic beat The third beat represents the postextrasystolic beat There is substantial improvement in systolic shortening on both length gauges End diastolic segment length and end diastolic left ventricular pressure are unchanged AP = aortic pressure LVP = left ventricular pressure

mm Hg ( $p < 0.001$ ) Insignificant increases were noted in end diastolic left ventricular pressure from  $5.6 \pm 0.4$  to  $6.2 \pm 0.8$  mm Hg and segment length from  $10.8 \pm 1.2$  to  $11.1 \pm 1.3$  mm

The subsequent time course of responsiveness of the ischemic segment to PESP was observed over a period of three hours in nine dogs In seven of these dogs post occlusion pre extrasystolic shortening remained relatively stable while there was a progressive deterioration in PESP responsiveness (Figs 4 and 5) Thus, while PESP produced a 113 per cent mean increase in systolic shortening prior to occlusion, this response had decreased to only 5 per cent of resting shortening ( $p = NS$ ) at three hours In the other two dogs this progressive loss of responsiveness was not observed In one animal occlusion produced a reduction in resting function to only 50 per cent of control in the second, a substantial spontaneous return of function followed occlusion and stabilized at a level more than twice that of the remainder of the group For this reason these two animals were treated separately

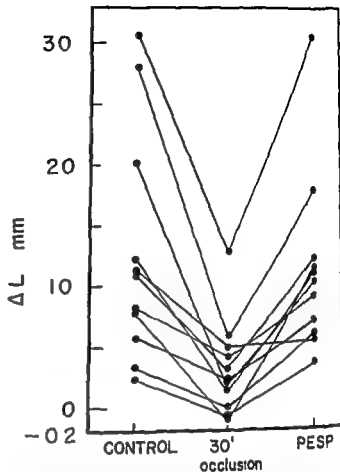


Fig 3 Post extrasystolic responsiveness of acutely ischemic myocardium Systolic shortening of the ischemic segment ( $\Delta L$ ) decreased significantly 30 minutes after coronary occlusion but improved to near preocclusion levels with post extrasystolic potentiation

## Discussion

This study demonstrates that atrial stimulation produces post extrasystolic potentiation of acutely ischemic myocardium even in the absence of resting shortening The degree of response to PESP was inversely related to the duration of ischemia Since no significant changes in left ventricular end diastolic pressure or segment length were observed the improvement in systolic shortening following PESP appears unrelated to changes in ventricular preload That the observed PESP responses occurred in part as a consequence of significant changes in left ventricular afterload is possible but doubtful aortic diastolic pressure decreased on the post extrasystolic beat due to the longer diastolic pause following the premature atrial stimulus, while systolic aortic pressure was augmented Because of these directionally opposite effects the total afterload could well have remained relatively unchanged Lastly since these pressure changes occurred for only a

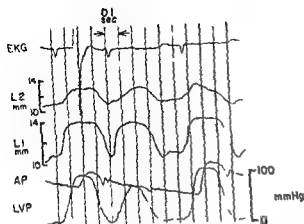


Fig 4 Loss of responsiveness to post extrasystolic potentiation. The data illustrated are from the same animal depicted in Fig 2 Two and one half hours after occlusion pre extrasystolic function is essentially unchanged and no shortening is seen on either length gauge (first beat). The central ischemic gauge (L) now fails to respond to the stimulus of PESP (third beat) while the adjacent gauge (L) continues to demonstrate improvement in systolic shortening.

single beat it is highly unlikely that regional function could have improved in response to augmented coronary flow especially in the face of total proximal occlusion. The observed responses in epicardial segment function therefore probably reflect primary changes in contractile state induced by PESP<sup>2,3</sup> rather than improved ventricular loading conditions or myocardial perfusion.

The epicardium is much less sensitive to the effects of ischemia than is the endocardium. The current data must be extrapolated to the intact heart only with caution therefore since the more profoundly ischemic deeper regions of myocardium may not respond in like fashion. On the other hand a number of clinical ventriculographic studies have demonstrated PFSP responsiveness of ischemic endocardium and pathologic studies reveal that such reversibly dysfunctional regions are histologically non-infarcted<sup>24</sup>. Therefore a substantial body of data suggests that the total loss of regional myocardial function secondary to ischemia need not be accompanied by muscle death and may in fact be completely reversible.

The mechanism responsible for the variable function of ischemic myocardium remains unknown. The magnitude of ischemia is not a simple

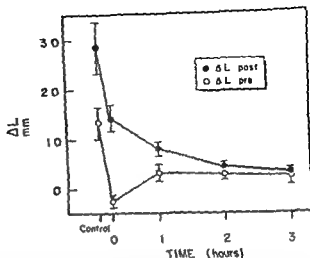


Fig 5 Time course of ischemic responsiveness to PESP. Mean ( $\pm 1$  SEM) systolic shortening ( $\Delta L$ ) of the ischemic zone is plotted against time after occlusion. The open circles represent the pre extrasystolic beat ( $\Delta L$  pre) and the solid circles and the post-extrasystolic beat ( $\Delta L$  post). Following occlusion pre-extrasystolic shortening decreases and remains depressed for the duration of the study. PESP produces a significant increase in systolic shortening for the first hour after occlusion but little change thereafter.

determinant of ischemic dysfunction since not only can deeply ischemic myocardium retain contractile behavior<sup>25</sup> but also remote nonischemic muscle may become depressed<sup>26</sup>. The duration of ischemia is also a complex determinant since reversible regional dysfunction probably persists for long periods of time in clinical ischemic heart disease<sup>12,13,14</sup>. In addition alterations of ventricular loading and contractility significantly influence ischemic segment function<sup>27,28</sup>. Although this study was not designed to investigate the mechanism of reversible dysfunction the observed time-dependency of PESP responsiveness emphasizes this complex interplay of factors.

If cardiac stimulation is to be used in either experimental studies or in clinical cardiology to detect and quantify reversibly dysfunctional potentially viable myocardium PFSP via atrial stimulation offers a number of substantial advantages in contrast to pharmacologic agents. The stimulus is safely easily and rapidly delivered. The dose is variable by alteration of coupling interval and is not limited by dose dependent side effects. The magnitude of the response is large, readily quantitated and highly reproducible. The effects are transient and do not increase myocar-

dial oxygen demand for more than 1 or 2 cardiac cycles. Finally, major changes in preload, afterload, and peripheral resistance do not persist following post extrasystolic potentiation.<sup>31</sup> The variables affecting segmental performance are thus more narrowly controlled than in the case with peripheral vasodilators or inotropic agents. For these reasons the method seems ideally suited for clinical use.

## Summary

The response of acutely ischemic myocardium to post extrasystolic potentiation (PESP) was evaluated in 11 mongrel dogs. Mercury in silastic length gauges were sutured to the epicardial surface of the left ventricle. Left ventricular pressure was determined via an apical large bore catheter-transducer system and controlled by volume manipulation. The anterior descending coronary artery was then ligated, and single premature atrial contractions were introduced via an external stimulator. Thirty minutes after occlusion, shortening during ejection had decreased an average of  $81 \pm 8$  per cent, from  $1.30 \pm 0.29$  to  $0.32 \pm 0.05$  mm. PESP initially induced a marked restoration toward normal segmental contraction as systolic shortening increased significantly to  $1.14 \pm 0.23$  mm. Additionally paradoxical systolic expansion, when present, reverted to a normal pattern of contraction during PESP. Responsiveness to PESP deteriorated progressively with time over 3 hours following occlusion until the muscle became essentially totally unresponsive to this stimulus. It is concluded that a single premature atrial beat may be used to induce PESP and provides an effective stimulus for contractile reserve of acutely dysfunctional ischemic myocardium. Loss of responsiveness to PESP may represent the progression to nonviability following acute ischemia.

The authors wish to acknowledge the editorial assistance of Mrs. Betty Garrigues.

## REFERENCES

1. Saliel J, Lesperance J, Bourassa M G, Castonguay Y, Campeau L, and Grondin P. Reversibility of left ventricular dysfunction following aorto-coronary bypass grafts. *Am J Roentgenol* 110:739 1970.
2. Pees G, Bristow J D, Kremkau E L, Green G S, Herr R H, Griswold H E, and Starr A. Influence of aortocoronary bypass surgery on left ventricular performance. *N Engl J Med* 284:1116 1971.
3. Chatterjee K, Swan H J C, Parmley W W, Sustaita H, Marcus H S, and Matloff J M. Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous vein bypass. *N Engl J Med* 286:1117 1972.
4. Chatterjee K, Swan H J C, Parmley W W, Sustaita H, Marcus H S, and Matloff J M. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. With and without previous myocardial infarction. *Circulation* 47:276 1973.
5. Hamby R I, Tabrah F, Aintablian A, Hartstern M L, and Wisoff B G. Left ventricular hemodynamics and contractile pattern after aortocoronary bypass surgery. *Am Heart J* 88:149 1974.
6. Rutherford B D, Gau G T, and Danielson G A. Left ventricular haemodynamics before and soon after saphenous vein bypass graft operation for angina pectoris. *Br Heart J* 34:1156 1972.
7. Arbogast R, Salagnac A, and Bourassa M G. Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction. *Am J Med* 54:290 1973.
8. Lapin E S, Murray J A, Bruce R A, and Wirtzschel L. Changes in maximal exercise performance in the evaluation of saphenous vein bypass surgery. *Circulation* 47:1164 1973.
9. Hammermeister K E, Kennedy W, Hamilton C W, Steward D L, Gould K L, Lipscomb K, and Marras J A. Aortocoronary saphenous vein bypass. Failure of successful grafting to improve resting left ventricular function in chronic angina. *N Engl J Med* 290:186 1974.
10. Hairston P, Newman W H, and Daniel H B. Myocardial contractile force as influenced by direct coronary surgery. *Ann Thorac Surg* 15:364 1973.
11. Boudoulas H, Lewis R P, Vasko J S, Karayannacos P E, and Beaver M M. Left ventricular function and adrenergic hyperactivity before and after saphenous vein bypass. *Circulation* 53:802 1976.
12. Helfant R H, Pine R, Meister S G, Feldman M S, Trout R G, and Banks V S. Nitroglycerin to unmask reversible asynergy. Correlation with post coronary bypass ventriculography. *Circulation* 50:108 1974.
13. McNulty J H, Hattenbauer M T, Rosch J, Kloster F E, and Rahumtools S H. Improvement in left ventricular wall motion abnormalities after nitroglycerin. *Circulation* 51:140 1975.
14. Banks V S, Bodenheimer M M, and Helfant R H. Determinants of reversible asynergy. Effect of pathologic Q waves, coronary collaterals, and anatomic location. *Circulation* 50:714 1974.
15. Reddy P, Curtis E I, O'Toole J D, Matthews R G, Salerno R, Leon D F, and Shaver J A. Reversibility of left ventricular asynergy by nitroglycerin in coronary artery disease. *Am Heart J* 90:479 1975.
16. Banks V S, Bodenheimer M M, Shah H, and Helfant R H. Intervention ventriculography. Comparative value of nitroglycerin, post extrasystolic potentiation, and nitroglycerin plus post extrasystolic potentiation. *Circulation* 53:632 1976.
17. Dyke S H, Cohn P F, Gorlin R, and Sonnenblick E H. Detection of residual myocardial function in coronary artery disease using post extrasystolic potentiation. *Circulation* 50:694 1974.
18. Hamby R I, Aintablian A, Wisoff B G, and Hartstern M L. Response of the left ventricle in coronary artery disease to post-extrasystolic potentiation. *Circulation* 51:428 1975.
19. Cohn P F, Gorlin R, German M V, Sonnenblick

- E H Horn H R Cohn I H and Collier J J Jr  
Relation between contractile reserve and prognosis in  
patients with coronary artery disease and a depressed  
ejection fraction *Circulation* 51 414 19 5
- 20 Schellbert H R Covell J W Burns J W, Maroko  
P R and Ross J Jr Observations on factors affecting  
local forces in the left ventricular wall during acute  
myocardial ischemia *Circ Res* 33 306 19 1
- 21 Dyke S H Urschel C W Sonnenblick E H Gorlin  
R and Cohn P F Detection of latent function in  
acutely ischemic myocardium in the dog Comparison of  
pharmacologic inotropic stimulation and post extrasys-  
tolic potentiation *Circ Res* 36 490 19 5
- 22 da Luz P L Forrester J S Wyatt H L Tyberg J V  
Chagrasuhs R Parmley W W and Swan H J C  
Hemodynamic and metabolic effects of sodium nitro-  
prusside on the performance and metabolism of regional  
ischemic myocardium *Circulation* 52 400 19 5
- 23 Theroux P Franklin D Ross J Jr and Kemper  
W S Regional myocardial function during acute coro-  
nary artery occlusion and its modification by pharmaco-  
logic agents in the dog *Circ Res* 35 896 19 4
- 24 Chamberlain D A Leimbach R C and Sanders C A  
The effect of paired atrial pacing on left atrial and  
ventricular performance in the dog *Cardiovasc Res*  
4 116 19 0
- 25 Grossman W Cardiac catheterization and angiography  
Philadelphia 1974 Lea & Febiger p 78
- 26 Tyberg J V Forrester J S Wyatt H L Goldner  
S J Parmley W W and Swan H J C An analysis of  
segmental ischemic dysfunction utilizing the pres-  
sure length loop *Circulation* 49 748 1974
- 27 Forrester J S Tyberg J V Wyatt H L Goldner  
S J Parmley W W and Swan H J C The pres-  
sure-length loop A new method for simultaneous  
measurement of segmental and total cardiac function *J*  
*Appl Physiol* 37 771 1974
- 28 Wyatt H L, da Luz P L Forrester J S Diamond  
G A Chagrasuhs R, and Swan H J C Functional  
abnormalities in nonoccluded regions of myocardium  
after experimental coronary occlusion *Am J Cardiol*  
37 388 19 6
- 29 Forrester J S Wyatt H L Tyberg J V da Luz P L,  
Diamond G A and Swan H J C Functional signifi-  
cance of regional ischemic contraction abnormalities  
*Circulation* 54 64 19 6
- 30 Cranefield P F The force of contraction of extrasys-  
tolic and the potentiation of force of the postextrasys-  
tolic contraction A historical review *Bull N Y Acad*  
*Med* 41 419 1965
- 31 Hoffman B F, Bundler E., and Suckling E W Postex-  
trasystolic potentiation of contraction in cardiac muscle  
*Am J Physiol* 185 90 19 6
- 32 Hoffman B F Bartelstone H J Scherlag H J and  
Cranefield P F Effects of postextrasystolic potentia-  
tion on normal and failing hearts *Bull N Y Acad Med*  
41 498 1965
- 33 Peck W., Chesler E and Schrire V Post-extrasystolic  
ventricular pressure responses *Circulation* 44 523  
1971
- 34 Cox J L Daniel T M and Boineau J P The  
electrophysiologic time-course of acute myocardial  
ischemia and the effects of early coronary artery perfu-  
sion *Circulation* 48 971 1973
- 35 Dyke S H Kirk E S and Sonnenblick E H  
Heterogeneous transmural function in ischemia  
*Clin Res* 20 3 0 19 2
- 36 Bodenheimer M M Banks V S Hermann C A  
Trout R G Pasdar H and Helfant R H Reversible  
asymmetry Histopathologic and electrographic correla-  
tions in patients with coronary artery disease *Circula-  
tion* 53 797 19 6
- 37 Jennings R B and Ganote C E Structural changes in  
myocardium during acute ischemia *Circ Res* 34 and  
35 III 156 19 4
- 38 Hood W B Jr Covell, V H Abelmann W H., and  
Norman J C Persistence of contractile behaviour in  
acutely ischemic myocardium *Cardiovasc Res* 3 249  
1969
- 39 Horn H R Teichholz L E Cohn P F Herman  
M V and Gorlin R Augmentation of left ventricular  
contraction pattern in coronary artery disease by an  
inotropic catecholamine The epinephrine ventriculo-  
gram *Circulation* 49 1063 1974
- 40 Wyatt H L, da Luz P L Waters D D Swan H J C  
and Forrester J S Contrasting influences of alterations  
in ventricular preload and afterload upon systemic  
hemodynamics, function and metabolism of ischemic  
myocardium *Circulation* (in press)



dial oxygen demand for more than 1 or 2 cardiac cycles. Finally, major changes in preload, afterload, and peripheral resistance do not persist following post extrasystolic potentiation.<sup>13</sup> The variables affecting segmental performance are, thus, more narrowly controlled than is the case with peripheral vasodilators or inotropic agents. For these reasons, the method seems ideally suited for clinical use.

## Summary

The response of acutely ischemic myocardium to post extrasystolic potentiation (PESP) was evaluated in 11 mongrel dogs. Mercury in silastic length gauges were sutured to the epicardial surface of the left ventricle; left ventricular pressure was determined via an apical large bore catheter-transducer system and controlled by volume manipulation. The anterior descending coronary artery was then ligated, and single premature atrial contractions were introduced via an external stimulator. Thirty minutes after occlusion, shortening during ejection had decreased an average of  $81 \pm 8$  per cent from  $1.30 \pm 0.29$  to  $0.32 \pm 0.05$  mm. PESP initially induced a marked restoration toward normal segmental contraction as systolic shortening increased significantly to  $1.14 \pm 0.23$  mm. Additionally, paradoxical systolic expansion when present reverted to a normal pattern of contraction during PESP. Responsiveness to PESP deteriorated progressively with time over 3 hours following occlusion until the muscle became essentially totally unresponsive to this stimulus. It is concluded that a single premature atrial beat may be used to induce PESP and provides an effective stimulus for contractile reserve of acutely dysfunctional ischemic myocardium. Loss of responsiveness to PESP may represent the progression to nonviability following acute ischemia.

The authors wish to acknowledge the editorial assistance of Mrs. Betty Garrigue.

## REFERENCES

1. Saltiel J, Lesperance J, Bourassa M G, Castonguay Y, Campeau L, and Grondin P. Reversibility of left ventricular dysfunction following aorto-coronary bypass grafts. *Am J Roentgenol* 110: 739-1970.
2. Rees G, Brinow J D, Kremkau E L, Green G S, Herr N H, Griswold H E, and Starr A. Influence of aortocoronary bypass surgery on left ventricular performance. *N Engl J Med* 284: 1116-1971.
3. Chatterjee K, Swan H J C, Parmley W W, Sustaita H, Marcus H S, and Matloff J M. Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous vein bypass. *N Engl J Med* 286: 1117, 1972.
4. Chatterjee K, Swan H J C, Parmley W W, Sustaita H, Marcus H S, and Matloff J M. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. With and without previous myocardial infarction. *Circulation* 47: 276-1973.
5. Hamby R I, Tabrah F, Antablian A, Harsten M L, and Wisoff H G. Left ventricular hemodynamics and contractile pattern after aortocoronary bypass surgery. *Am Heart J* 88: 149-1974.
6. Rutherford H D, Gau G T, and Danielson G K. Left ventricular haemodynamics before and soon after saphenous vein bypass graft operation for angina pectoris. *Br Heart J* 34: 1156-1972.
7. Arbogast H, Salagnac A, and Bourassa M G. Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction. *Am J Med* 54: 290-1973.
8. Lapin E S, Murray J A, Bruce R A, and Winterfeld L. Changes in maximal exercise performance in the evaluation of saphenous vein bypass surgery. *Circulation* 47: 1164-1973.
9. Hammermeister K E, Kennedy W, Hamilton G W, Steward D L, Gould K L, Lipscomb K, and Marras J A. Aortocoronary saphenous vein bypass. Failure of successful grafting to improve resting left ventricular function in chronic angina. *N Engl J Med* 280: 156-1974.
10. Harsten M L, Newman W H, and Damell H B. Myocardial contractile force as influenced by direct coronary surgery. *Ann Thorac Surg* 15: 364-1973.
11. Boudoulas H, Lewis R P, Vasko J S, Karayannacos P E, and Beaver B M. Left ventricular function and adrenergic hyperactivity before and after saphenous vein bypass. *Circulation* 53: 802-1976.
12. Helfant R H, Fine R, Meister S G, Feldman M S, Trout R G, and Banks V S. Nitroglycerin to unmask reversible asynergy. Correlation with post coronary bypass ventriculography. *Circulation* 50: 108-1974.
13. McAnulty J H, Hattenbauer M T, Rosch J, Kloster F E, and Rahmtoola S H. Improvement in left ventricular wall motion abnormalities after nitroglycerin. *Circulation* 51: 140-1975.
14. Banks V S, Bodenheimer M M, and Helfant R H. Determinants of reversible asynergy. Effect of pythogenic Q waves, coronary collaterals, and anatomic location. *Circulation* 50: 714-1974.
15. Reddy S P, Curtiss E I, O'Toole J D, Matthews R G, Salerno P, Leon D F, and Shaver J A. Reversibility of left ventricular asynergy by nitroglycerin in coronary artery disease. *Am Heart J* 90: 479-1975.
16. Banks V S, Bodenheimer M M, Shah R, and Helfant R H. Intervention ventriculography. Comparative value of nitroglycerin post extrasystolic potentiation and nitroglycerin plus post extrasystolic potentiation. *Circulation* 53: 632-1976.
17. Dyke S H, Cohn P F, Gorlin R J, and Sonnenblick E H. Detection of residual myocardial function in coronary artery disease using post extrasystolic potentiation. *Circulation* 50: 694-1974.
18. Hamby R I, Antablian A, Wisoff H G, and Harsten M L. Response of the left ventricle in coronary artery disease to post extrasystolic potentiation. *Circulation* 51: 428-1975.
19. Cohn P F, Gorlin R, German M V, Sonnenblick

- E H Horn H R Cohn L H, and Collier J J Jr Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction *Circulation* 51 414 1975
- 90 Schelbert H R Covell J W Burns J W Maroko P R and Ross J Jr Observations on factors affecting local forces in the left ventricular wall during acute myocardial ischemia *Circ Res* 29 306 1971
- 21 Dyke S H Urschel C W, Sonnenblick E H Gorlin R and Cohn P F Detection of latent function in acutely ischemic myocardium in the dog: Comparison of pharmacologic inotropic stimulation and post-extrasystolic potentiation *Circ Res* 36 490 1975
- 92 de Luz P L, Forrester J S Wyatt H L Tyberg J V Chagrasulis R Parmley W W, and Swan H J C Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium *Circulation* 52 400 1975
- 23 Theroux P Franklin D Ross J, Jr and Kemper W S Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog *Circ Res* 35 896 1974
- 4 Chamberlain D A Leinbach R C and Sanders C A The effect of paired atrial pacing on left atrial and ventricular performance in the dog *Cardiovasc Res* 4 116, 19 11
- 25 Grossman, W. Cardiac catheterization and angiography Philadelphia 1974 Lea & Febiger p 78.
- 26 Tyberg J V, Forrester J S Wyatt H L Goldner S J Parmley W W, and Swan H J C An analysis of segmental ischemic dysfunction utilizing the pressure length loop *Circulation* 49 743, 1974
- 27 Forrester J S Tyberg J V, Wyatt H L, Goldner S J Parmley W W, and Swan H J C The pressure length loop: A new method for simultaneous measurement of segmental and total cardiac function *J Appl Physiol* 37 771 1974
- 94 Wyatt H L, de Luz P L, Forrester J S Diamond G A Chagrasulis R and Swan H J C Functional abnormalities in nonoccluded regions of myocardium after experimental coronary occlusion *Am J Cardiol* 37 366 1976
- 29 Forrester J S Wyatt H L Tyberg J V de Luz P L Diamond G A and Swan H J C Functional significance of regional ischemic contraction abnormalities *Circulation* 54 61 19 6
- 30 Cranefield P F The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contraction: A historical review *Bull. N Y Acad Med* 41 419 1965
- 31 Hoffman B F Bindler H and Suckling E E Postextrasystolic potentiation of contraction in cardiac muscle *Am J Physiol* 185 95 1956
- 32 Hoffman B F Bartelstone H J Scherlag B J, and Cranefield P F Effects of postextrasystolic potentiation on normal and failing hearts *Bull N Y Acad. Med.* 41 498 1965
- 33 Peck W, Chesler E and Schurr V Post-extrasystolic ventricular pressure responses *Circulation* 44 523 1971
- 34 Cox J L Daniel T M and Boineau J P The electrophysiologic time-course of acute myocardial ischemia and the effects of early coronary artery perfusion *Circulation* 48 971 1973
- 35 Dyke S H Kirk E S and Sonnenblick H Heterogeneous transmural function in ischemia *Circ Res* 20 370 1972
- 36 Bodenheimer M M Banks V S Hermann G A Trout R H Pasdar H and Helfant R H Reversible asynergy: Histopathologic and electrographic correlations in patients with coronary artery disease *Circulation* 53 192 1976
- 37 Jennings R B and Ganote C E Structural changes in myocardium during acute ischemia *Circ Res* 34 and 35 III 156 1974
- 38 Hood W B Jr Covell V H Abelman W R, and Norman, J C Persistence of contractile behaviour in acutely ischemic myocardium *Cardiovasc Res* 3 249 1969
- 39 Horn H R, Teichholz L E Cohn P F Herman M V and Gorlin R Augmentation of left ventricular contraction pattern in coronary artery disease by an inotropic catecholamine The epinephrine ventriculogram *Circulation* 49 1063 1974
- 40 Wyatt H L de Luz P L, Waters D D Swan H J C and Forrester J S Contrasting influences of alterations in ventricular preload and afterload upon systemic hemodynamics, function and metabolism of ischemic myocardium *Circulation* (In press)

# Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease

B E Strauer

A Scherpe

Munich, W Germany

A primary action of nitroglycerin is to relax vascular smooth muscle. Accordingly, alterations in regional and systemic flow, venous pooling and changes in arteriolar and venous resistance may occur.<sup>1-4</sup> Furthermore it has been suggested that nitroglycerin may also exert direct or indirect inotropic effects in isolated heart muscle preparations,<sup>5,6</sup> as well as in the intact heart.<sup>7-9</sup> The quantitative evaluation of both the vasodilator and contractile properties of sublingual nitroglycerin in man is impeded by the rapidly fluctuating unsteady state which is evoked because of the multiple sites of action and the secondary effects they produce.<sup>10</sup> This study was designed to describe the effects on coronary subjects of intravenously infused nitroglycerin on left ventricular function and coronary blood flow, and on the systemic vascular pooling capacity.

## Material and methods

Studies were carried out in 14 coronary patients: eight males and six females with a mean age of 48.8 years (range 29 to 62 years) (Table I). All patients gave informed consent for this study according to the declaration of Helsinki.<sup>11</sup> Measurements were performed prior to the application of any contrast medium. Left ventricular and aortic pressures were measured through catheters (pigtail, Cordis) which were directly connected to pressure transducers (Statham P23 Gb). The catheter system had a natural frequency

above 20 Hz and a phase lag linear with frequency in this frequency range. Overshoots as well as motion artifacts were not present at rest nor under the pharmacological studies. All pressures were referred to zero level 10 cm above the table top. Peak ( $dp/dt/P$ ) was calculated by dividing the maximum rate of pressure development by its corresponding total isovolumic pressure. Heart rate was kept constant at 10 to 15 per cent above individual spontaneous frequency by atrial pacing using a bipolar electrode and an external cardiac pacing device. The pacing catheter was also used for the intravenous infusions. A Goodale-Lubin catheter (Ch. 7) was inserted through the left cubital vein and introduced into the coronary sinus for coronary sinus blood sampling and for coronary blood flow determinations and a second venous catheter was placed into the pulmonary artery for continuous pressure measurement. Since in our laboratory both the coronary sinus and pulmonary artery catheters are routinely introduced catheters in coronary patients, the external atrial pacing device was the only additionally introduced catheter in these patients. Cardiac output was determined by thermodilution by the use of a modification of the method of Warner and Wood.<sup>12</sup> Stroke work index, total peripheral resistance, and pulmonary vascular resistance were calculated by standard formulae.<sup>13</sup>

Total coronary blood flow of the left ventricle ( $V$ ) was determined by the argon inert gas method with gas chromatographic analysis of argon in arterial and coronary venous blood (Varian GmbH, Darmstadt/GFR). Details of this method have been previously described.<sup>14,15</sup> Left ventricular oxygen consumption ( $MVO_2$ ) has been calculated as the product of coronary blood

From the Department of Medicine, University of Munich.

Supported by Deutsche Forschungsgemeinschaft.

Received for publication June 1, 1977.

Accepted for publication Sept. 19, 1977.

Reprint requests: Priv. Doz. Dr. B. E. Strauer, Department of Medicine, University of Munich, Klinikum Grosshadern, Marchionnistrasse 15, D-8000 Munich 70/W, Germany.

flow (ml per min  $\times 100$  Gm) and the arterial-coronary venous oxygen difference (avDO). Arterial and coronary venous oxygen saturations have been measured by CO oxymetry.

Hemodynamic measurements were performed (1) under control conditions with two sets of control measurements taken at least 5 minutes apart (Table II) (2) under nitroglycerin infusion which was begun at 30 mcg./min. and increased stepwise until systolic left ventricular or aortic pressure fell by an average of 20 per cent. The infusion rate and maintenance dose necessary to continuously lower systolic left ventricular pressure by an average of 20 per cent was 62 mcg./min. (range 40 to 92 mcg./min.). The infusion was then continued and two sets of hemodynamic measurements were obtained at 5 minute intervals (Table II) (3) under the infusion of dextran parallel to the infusion of nitroglycerin. Dextran (Macrodex Knoll AG/GFR) was intravenously administered utilizing a Harvard pump (series 921) and was increased stepwise until left ventricular systolic and end diastolic pressure had reached the initial values that is the control values before nitroglycerin. At this level of restored pressure the infusion of both nitroglycerin and dextran was continued for 5 minutes to determine the hemodynamic parameters by two sets in 5 minute intervals. The amount of dextran necessary for the re-establishment of left ventricular pressure was then determined (mean 437 ml. in 20 to 28 minutes).

Coronary blood flow measurements were performed three times (1) under control conditions (2) under nitroglycerin infusion (3) under both nitroglycerin and dextran infusion within the period of restored left ventricular pressure.

Intravenous nitroglycerin was used as an aqueous dilution prepared from a specially produced 5 per cent sterile alcoholic nitroglycerin solution (Dynamit Nobel GmbH Köln/GFR). Statistical comparisons were made using Student's paired *t* test.

## Results

**Nitroglycerin infusion.** Under constant nitroglycerin infusion rate a 20 per cent decrease in systolic left ventricular pressure was associated with a 47 per cent decrease in left ventricular end diastolic pressure (Table III). Maximum rate of left ventricular pressure development (peak dp/dt)

Table I Patient population

| Patient no | Age (yr) | Sex | ECG-diagnosis      | Degree of stenosis |     |     |     |
|------------|----------|-----|--------------------|--------------------|-----|-----|-----|
|            |          |     |                    | MLCA               | LAD | LCx | RCA |
| 1          | 29       | M   | ST T wave changes  | 0                  | 3   | 3   | 3   |
| 2          | 48       | F   | Ant sept infarct   | 0                  | 4   | 2   | 4   |
| 3          | 52       | F   | Inf infarct        | 0                  | 2   | 4   | 3   |
| 4          | 46       | M   | Inf infarct        | 0                  | 4   | 4   | 3   |
| 5          | 62       | M   | Ant lat infarct    | 0                  | 4   | 4   | 2   |
| 6          | 51       | M   | ST T wave changes  | 0                  | 3   | 3   | 0   |
| 7          | 37       | M   | ST T wave changes  | 0                  | 4   | 3   | 0   |
| 8          | 31       | F   | Ant lat infarct    | 2                  | 4   | 2   | 4   |
| 9          | 61       | F   | Inf apical infarct | 0                  | 3   | 0   | 4   |
| 10         | 42       | M   | ST T wave changes  | 0                  | 3   | 4   | 2   |
| 11         | 58       | F   | Ant lat infarct    | 2                  | 4   | 4   | 0   |
| 12         | 56       | M   | Inf apical infarct | 0                  | 3   | 3   | 4   |
| 13         | 59       | F   | ST T wave changes  | 0                  | 3   | 3   | 3   |
| 14         | 52       | M   | Inf infarct        | 0                  | 3   | 3   | 4   |

Abbreviations: MLCA = main left coronary artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; ant = anterior; sept = septal; inf = inferior; lat = lateral.

Degree of stenosis by coronary arteriogram: 0 = normal; 1 = less than 50 per cent luminal narrowing; 2 = less than 5 per cent luminal narrowing; 3 = 5 per cent to 1 mm narrowing; 4 = complete obstruction.

dt) decreased by 13 per cent whereas peak (dp/dt/P) increased by 15 per cent. At constant heart rate the cardiac index and stroke volume index decreased by 16 per cent. As a consequence of the decreases of both stroke volume index and mean systolic pressure the stroke work index was reduced by 30 per cent (Table III). Total peripheral resistance index decreased by only 3 per cent whereas pulmonary vascular resistance index fell by 29 per cent. Coronary blood flow of the left ventricle significantly decreased following intravenous nitroglycerin infusion by 13 per cent (mean) in comparison with the controls and MVO, decreased by 15 per cent (Table III).

**Nitroglycerin plus dextran infusion.** The re-establishment of left ventricular systolic pressure during nitroglycerin infusion by the parallel infusion of dextran was associated with complete normalization of left ventricular end diastolic pressure. In contrast at comparable systolic and end-diastolic pressure and heart rate there were significant increases in peak dp/dt in pump parameters (stroke volume index, cardiac index, stroke work index) and in both coronary blood flow and MVO, (Table III, Fig 2). The increases in these values ranged 10 to 28 per cent above controls.

Table II Protocol for infusion of nitroglycerin and of both nitroglycerin and dextran

|                         | Controls    | NTG                           | NTG + dextran |
|-------------------------|-------------|-------------------------------|---------------|
| Hemodynamics            |             |                               |               |
| P <sub>L</sub>          | • •         | • •                           | • •           |
| P <sub>A1</sub>         | • •         | • •                           | • •           |
| P <sub>A2</sub>         | • •         | • •                           | • •           |
| CO                      | • •         | • •                           | • •           |
| Coronary blood flow     | • •         | • •                           | • •           |
| Arterial O saturation   | • •         | • •                           | • •           |
| Cor venous O saturation | • •         | • •                           | • •           |
| Hemoglobin              | • •         | • •                           | • •           |
| Hematocrit              | • •         | • •                           | • •           |
| Nitroglycerin infusion  |             | —————                         |               |
| Dextran infusion        |             |                               | —————         |
| Time [min]              | 18 5 0 5 10 | 15 20 25 30 35 40 45 50 55 60 |               |

**Vascular pooling capacity of nitroglycerin** The volume expansion necessary for the complete reestablishment of left ventricular pressures averaged 437 ml (Table III)

### Discussion

This study suggests that the hemodynamic effects of nitroglycerin in coronary artery disease are characterized by a moderate positive inotropic effect on the myocardium as well as by a diastolic and systolic unloading of the heart. After compensating for changes in heart rate as well as for nitroglycerin induced changes in left ventricular end diastolic pressure and afterload significant increases in left ventricular pump parameters, contractility indices as well as coronary blood flow and MVO were demonstrated. Thus by experimentally reversing some of the hemodynamic responses to nitroglycerin through control of heart rate, left ventricular end diastolic pressure, and afterload a direct effect of nitroglycerin on left ventricular performance and coronary blood flow was elicited. Finally, the vascular pooling effect of nitroglycerin has been quantitatively evaluated by the direct measurement of volume expansion necessary for the reestablishment of both left ventricular and pulmonary artery pressure during continuous nitroglycerin infusion.

**Nitroglycerin infusion** Systolic unloading was associated with a 3 per cent decrease in total peripheral resistance index. This may be attributed to the decreases in cardiac index (16 per cent) parallel to pressure change so that the calculated peripheral resistance index did not change significantly. In contrast pulmonary

vascular resistance index fell by 29 per cent. This difference indicates that the effect of intravenously administered nitroglycerin on pulmonary vascular resistance was far more pronounced than on the peripheral arterial vascular bed.

The decrease in stroke volume during nitroglycerin infusion at a fixed heart rate may be attributed primarily to a reduction in preload. This is indicated by the considerable decrease in left ventricular end diastolic pressure (-43 per cent) in these patients (Fig 1). Since spontaneous heart rate did not exceed the pacing rate obtained by the pacing device and basic heart rates at the end of the study (under the nitroglycerin plus dextran state) were essentially normal when compared with the control state, any baroreceptor mediated increases in heart rates can be excluded.

The decreases in coronary flow and in MVO during nitroglycerin may be related to the reductions of some of the major determinants of myocardial energy demand: "Wall tension which results as a consequence of ventricular pressure volume and wall thickness presumably was reduced because of the decrease in end diastolic (43 per cent) and systolic pressure (20 per cent) and in end diastolic volume." The external cardiac work was considerably reduced as evidenced by the decrease in left ventricular stroke work index (30 per cent). Thus two of the determinants of myocardial energy demand (tension cardiac work) were lowered and may be appropriate to explain the decrease in MVO. On the other hand left ventricular contractility was moderately enhanced under the influence of nitroglycerin (see below) and an increase in

contractility has been found associated with an increase in  $MVO_2$ .<sup>1,20</sup> However it may be reasonable to assume that the reductions in wall tension and in stroke work quantitatively override the increase in contractility as related to the ventricular energy demand so that a net decrease in the over all oxygen consumption occurred.

**Nitroglycerin plus dextran infusion** Re-establishment of left ventricular pressures through volume expansion (mean 437 ml) by dextran conceivably could influence ventricular and systemic hemodynamics as a specific result of dextran. The hematocrit was decreased non-significantly by 2 per cent (mean) which does not affect hemodynamics.<sup>1,2</sup> Likewise primary effects of dextran on blood viscosity as well as changes in vascular reactivity in erythrocyte characteristics and in cellular aggregation which may alter blood viscosity can be largely excluded since a 2 per cent reduction from normal hematocrit reduces blood viscosity (shear rate 20/sec) by approximately 1 to 3 centipoise<sup>2</sup> that is by 2 to 6 per cent. These small viscosity changes induced by dextran seem to have no effect on contractile function and hemodynamics *in situ*.<sup>3</sup> On the other hand infusion of dextran in coronary patients may exert an increase in left ventricular pressures with or without changes in stroke volume.<sup>2</sup> However these changes occurred when starting from control conditions whereas in this study dextran was exclusively used to restore left ventricular pressures to the initial values. Accordingly it seems unlikely that pressure changes may have contributed to the changes in left ventricular function and coronary hemodynamics. Moreover utilizing comparable infusion rates of dextran as in this study Khaja and colleagues<sup>4</sup> found no alterations in left ventricular contractility indices in coronary patients at fixed heart rate and stroke volume index increased only if the left ventricular end diastolic pressure was raised. However in none of the 14 patients of this study did left ventricular end diastolic pressure under the infusion of both nitroglycerin and dextran exceed the control values before nitroglycerin. Thus the procedure of restoring the nitroglycerin induced pressure decrease by dextran infusion (under atrial pacing) seems appropriate to examine the effects of nitroglycerin on ventricular performance independent of parallel changes in systolic and end-diastolic pressures and on heart rate.

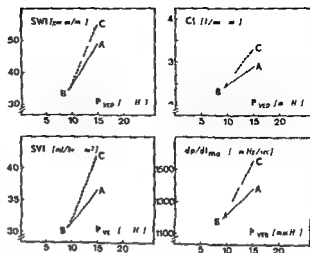


Fig 1 Relationships between left ventricular end-diastolic pressure and hemodynamic measures. The base and peak of the arrows indicates mean values from all patients. A = controls B = nitroglycerin infusion C = nitroglycerin plus dextran infusion.

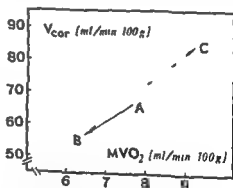


Fig 2 Left ventricular oxygen consumption ( $MVO_2$ ) and coronary blood flow ( $V_{cor}$ ). The base and peak of the arrows indicates mean values from all patients. A = controls B = nitroglycerin infusion C = nitroglycerin plus dextran infusion.

The combined nitroglycerin plus dextran infusion indicates that nitroglycerin itself moderately increases myocardial contractility. The rise in stroke volume index (14 per cent) and in cardiac index (13 per cent) occurred at constant end diastolic pressure afterload and heart rate when compared with the initial values. Secondly the rate of left ventricular pressure development as indicated by the rise in peak  $dp/dt$  (12 per cent) was increased. Thirdly peak  $(dp/dt/P)$  which under the influence of nitroglycerin alone possibly may have been overestimated because of the marked fall in left ventricular end diastolic pressure<sup>2</sup> was significantly enhanced under nitro-

Table III Hemodynamic findings in 14 patients receiving intravenous nitroglycerin as well as intravenous nitroglycerin and dextran

| Patient no |         | $P_L$<br>[mm Hg] | $P_{LVR}$<br>[mm Hg] | Peak $dp/dt$<br>[mm Hg/sec] | Peak $(dp/dt/P)$<br>[1/sec] | CI<br>[L/min m <sup>2</sup> ] | SVI<br>[ml/beat m <sup>2</sup> ] |
|------------|---------|------------------|----------------------|-----------------------------|-----------------------------|-------------------------------|----------------------------------|
| 1          | C       | 110              | 10                   | 1400                        | 24                          | 2.52                          | 33.0                             |
|            | NTG     | 85               | 5                    | 1250                        | 27                          | 2.21                          | 30.0                             |
|            | NTG + D | 115              | 10                   | 1600                        | 28                          | 3.47                          | 41.5                             |
| 2          |         | 138              | 8                    | 2300                        | 28                          | 3.36                          | 34.4                             |
|            |         | 92               | 5                    | 1650                        | 32                          | 2.51                          | 29.1                             |
|            |         | 135              | 8                    | 2900                        | 32                          | 3.59                          | 37.2                             |
| 3          |         | 105              | 20                   | 1000                        | 19                          | 3.18                          | 38.9                             |
|            |         | 110              | 12                   | 950                         | 25                          | 2.4                           | 29                               |
|            |         | 112              | 20                   | 1250                        | 26                          | 3.42                          | 41.1                             |
| 4          |         | 108              | 8                    | 1350                        | 18                          | 2.38                          | 33.9                             |
|            |         | 89               | 5                    | 1100                        | 22                          | 1.92                          | 28.9                             |
|            |         | 108              | 8                    | 1750                        | 24                          | 3.42                          | 41.1                             |
| 5          |         | 118              | 12                   | 950                         | 17                          | 2.76                          | 39.1                             |
|            |         | 85               | 8                    | 750                         | 20                          | 2.39                          | 33.1                             |
|            |         | 116              | 12                   | 1000                        | 21                          | 3.02                          | 42.4                             |
| 6          |         | 132              | 20                   | 1750                        | 29                          | 3.64                          | 48.9                             |
|            |         | 105              | 10                   | 1900                        | 33                          | 3.48                          | 47.3                             |
|            |         | 120              | 20                   | 1900                        | 33                          | 3.45                          | 46.8                             |
| 7          |         | 130              | 16                   | 1100                        | 19                          | 2.73                          | 33.0                             |
|            |         | 110              | 12                   | 1000                        | 18                          | 1.88                          | 22.1                             |
|            |         | 112              | 16                   | 1100                        | 20                          | 2.73                          | 33.0                             |

Abbreviations: C = control; NTG = nitroglycerin infusion; D = dextran infusion;  $P_L$  = peak systolic left ventricular pressure;  $P_{LVR}$  = left ventricular end diastolic pressure; peak  $dp/dt$  = maximum rate of left ventricular pressure development; peak  $(dp/dt/P)$  = ratio between the maximum rate of left ventricular pressure development and its isovolumic total pressure; CI = cardiac index; SVI = stroke volume index; SWI = stroke work index;  $\dot{V}O_2$  = oxygen consumption of the left ventricle; MVO = oxygen consumption of the left ventricle; SD = standard deviation; P values represent the difference between C and NTG infusion, or between C and both NTG and D infusion, as calculated by the paired Student's t test; NS = not significant; %  $\Delta$  average per cent change between C and NTG or between C and (NTG plus D).

glycerin at normal left ventricular end diastolic and systolic pressure (18 per cent). Thus, the changes in isovolumic contractility indices (peak  $dp/dt$ , peak  $[dp/dt/P]$ ) indicate increased isovolumic contraction velocity,<sup>21</sup> whereas the changes in stroke volume index indicate increased autotonic performance. There are theoretical objections to determination of  $dp/dt$  and peak  $(dp/dt/P)$  with an external transducer (pigtail catheter and Statham transducer). However, direct in vivo comparison with a catheter tip manometer at heart rates of 75 to 150/minute has shown that the two methods correspond closely to a value of 2000 mm Hg/sec.<sup>22</sup> Except for patient No. 2 this value has not been reached in this study.

It may be of interest that other clinical studies also suggest an inotropic action of nitroglycerin as evidenced by alterations in ejection fraction, wall motion, velocity of circumferential fiber shortening, or rate of left ventricular pressure

development.<sup>23-25</sup> However, evaluation of contractility in situ may be difficult because of the simultaneous alterations of hemodynamic variables after sublingual nitroglycerin.<sup>2</sup> On the other hand, a possible increase in ventricular compliance could increase diastolic volume at a given diastolic pressure. This could lead to an increased wall tension at a given afterload and end diastolic pressure which in turn could be responsible for the observed increases in contractility. However, a change in compliance has not yet been established in man under the influence of nitroglycerin, and there are no alterations in the length-tension relationships of isolated cat and human ventricular myocardium.<sup>26-28</sup> The assumption of a direct positive inotropic effect of nitroglycerin is substantiated by studies in animal experiments and in the isolated human atrial and ventricular myocardium in which increases of the extent of shortening of the

| SWI<br>[gm m/m] | HR<br>[beats/min] | TPRI<br>[mm Hg/min/L m] | PVRI<br>[mm Hg/min/L m] | V<br>[ml/min 100 g] | MVO<br>[ml/min 100 g] | Volume infused<br>[ml] |
|-----------------|-------------------|-------------------------|-------------------------|---------------------|-----------------------|------------------------|
| 45.2            | 73                | 34.9                    | 66                      | 76                  | 90                    | 500                    |
| 30.6            |                   | 30.1                    | 52                      | 72                  | 80                    |                        |
| 64.6            |                   | 26.0                    | 47                      | 112                 | 118                   |                        |
| 58.5            | 97                | 31.5                    | 51                      | 60                  | 75                    | 200                    |
| 28.6            |                   | 26.9                    | 56                      | 50                  | 59                    |                        |
| 61.7            |                   | 29.1                    | 47                      | 110                 | 114                   |                        |
| 40.3            | 89                | 27.3                    | 41                      | 63                  | 74                    | 150                    |
| 32.7            |                   | 34.0                    | 21                      | 59                  | 66                    |                        |
| 49.4            |                   | 26.4                    | 38                      | 72                  | 78                    |                        |
| 43.3            | 10                | 34.5                    | 59                      | 55                  | 56                    | 400                    |
| 71.0            |                   | 35.4                    | 52                      | 44                  | 44                    |                        |
| 60.4            |                   | 24.0                    | 41                      | 45                  | 58                    |                        |
| 53.7            | 71                | 32.9                    | 65                      | —                   | —                     | 315                    |
| 33.0            |                   | 27.8                    | 49                      | —                   | —                     |                        |
| 51.1            |                   | 28.3                    | 60                      | —                   | —                     |                        |
| 71.2            | 74                | 28.1                    | 63                      | 73                  | 81                    | 575                    |
| 57.9            |                   | 23.5                    | 37                      | 71                  | 89                    |                        |
| 60.6            |                   | 27.0                    | 67                      | 88                  | 62                    |                        |
| 48.9            | 83                | 28.5                    | 62                      | 59                  | 88                    | 500                    |
| 28.7            |                   | 47.0                    | 53                      | 50                  | 57                    |                        |
| 40.8            |                   | 33.8                    | 62                      | 60                  | 91                    |                        |

velocities of isotonic concentration and relaxation and of the rate of isometric tension development in afterloaded and in isometric studies have been demonstrated.<sup>1</sup> The increases in these parameters which were found at constant preload afterload and frequency of stimulation varied 12 to 27 per cent in comparison with the controls. Moreover equivalent shifts of the force-velocity relationships of both concentration and relaxation to higher values of velocity and tension occurred at constant preload.

The increase in total coronary blood flow (28 per cent) may be the consequence of direct coronary dilation or an increased myocardial energy demand. Since arterial-coronary venous oxygen difference was nearly unchanged it seems unlikely that the total coronary blood flow increased primarily due to coronary dilation. The increase in MVO indicates increased metabolic activity which is evidenced by the almost equal increases in both coronary blood flow (V) and myocardial oxygen consumption (MVO) (Fig. 2). Under nitroglycerin plus dextran both tension development and heart rate may be neglected as to their influence on the overall oxygen

consumption since they were controlled (heart rate) or presumably normalized (tension). Accordingly contractility and fiber shortening increased significantly and may contribute to the increased energy demand under the influence of nitroglycerin at stabilized pressures. In this regard the assumption of oxygen wasting<sup>10</sup> may be unnecessary since the coronary and metabolic effects occurred in quantitative accordance with changes of mechanical or contractile function of the left ventricle.<sup>2, 11</sup>

**Vascular pooling capacity.** The systemic vascular pooling capacity of nitroglycerin has been quantitatively determined during restoration of left ventricular end diastolic and systolic pressure by the infusion of dextran parallel to nitroglycerin infusion. The internal phlebectomy induced by nitroglycerin averaged  $437 \pm 128$  ml at an infusion rate of 62 mcg/minute (mean). This vascular pooling probably is due to venodilation.<sup>2</sup> The vascular pooling capacity provides an explanation for the fall in cardiac output and in derived measures (cardiac index, stroke volume index) as well as for the decreases in left ventricular systolic end diastolic and in pulmonary



Table III continued

| Patient no                 | $P_{LA}$<br>[mm Hg] | $P_{L+1}$<br>[mm Hg] | Peak $dp/dt$<br>[mm Hg/sec] | Peak $(dp/dt/P)$<br>[1/sec] | CI<br>[L/min m]    | QI<br>[mL/beat m] |
|----------------------------|---------------------|----------------------|-----------------------------|-----------------------------|--------------------|-------------------|
| 8                          | 108                 | 16                   | 900                         | 23                          | 3.11               | 470               |
|                            | 90                  | 9                    | 780                         | 26                          | 3.03               | 410               |
|                            | 104                 | 17                   | 900                         | 27                          | 3.39               | 460               |
| 9                          | 96                  | 17                   | 1300                        | 26                          | 2.54               | 282               |
|                            | 83                  | 10                   | 1200                        | 30                          | 1.70               | 195               |
|                            | 100                 | 16                   | 1400                        | 29                          | 3.21               | 359               |
| 10                         | 120                 | 18                   | 1650                        | 22                          | 2.6                | 361               |
|                            | 90                  | 10                   | 1100                        | 28                          | 2.14               | 291               |
|                            | 120                 | 18                   | 1900                        | 28                          | 2.64               | 371               |
| 11                         | 112                 | 12                   | 1500                        | 21                          | 3.34               | 345               |
|                            | 90                  | 8                    | 1280                        | 23                          | 3.03               | 315               |
|                            | 117                 | 13                   | 1600                        | 22                          | 3.74               | 449               |
| 12                         | 120                 | 12                   | 1520                        | 22                          | 3.08               | 303               |
|                            | 106                 | 8                    | 1320                        | 25                          | 2.97               | 261               |
|                            | 120                 | 12                   | 1520                        | 27                          | 3.97               | 388               |
| 13                         | 130                 | 20                   | 1300                        | 24                          | 2.71               | 388               |
|                            | 108                 | 11                   | 1400                        | 26                          | 2.4                | 339               |
|                            | 128                 | 20                   | 1500                        | 27                          | 2.71               | 389               |
| 14                         | 120                 | 17                   | 1300                        | 22                          | 2.66               | 360               |
|                            | 90                  | 7                    | 1100                        | 27                          | 1.99               | 250               |
|                            | 105                 | 16                   | 1400                        | 28                          | 3.16               | 415               |
| Mean $\pm$ SE<br>(Control) | 118<br>$\pm 12$     | 15<br>$\pm 4$        | 1380<br>$\pm 368$           | 22.4<br>$\pm 3.6$           | 2.89<br>$\pm 0.39$ | 364<br>$\pm 51$   |
| Mean $\pm$ SE<br>(NTG)     | 94<br>$\pm 9$       | 8<br>$\pm 2$         | 1199<br>$\pm 312$           | 25.9<br>$\pm 4.2$           | 2.44<br>$\pm 0.52$ | 306<br>$\pm 71$   |
| P value                    | $<0.001$            | $<0.001$             | $<0.01$                     | $<0.001$                    | $<0.001$           | $<0.001$          |
| % $\Delta$                 | -20%                | -43%                 | -13%                        | +15%                        | -16%               | -15%              |
| Mean $\pm$ SE<br>(NTG + D) | 115<br>$\pm 9$      | 15<br>$\pm 4$        | 1551<br>$\pm 494$           | 26.6<br>$\pm 3.6$           | 3.28<br>$\pm 0.39$ | 415<br>$\pm 41$   |
| P value                    | NS                  | NS                   | $<0.005$                    | $<0.001$                    | $<0.005$           | $<0.005$          |
| % $\Delta$                 | -2%                 | $\pm 0\%$            | +12%                        | +18%                        | +13%               | +14%              |

artery pressures. Similarly, this effect may also account for diminution of ventricular size observed in man<sup>17</sup> and may help to explain the beneficial action of nitroglycerin in some patients with acute left ventricular failure and pulmonary edema.<sup>2-10</sup> In these conditions marked elevations of left ventricular end diastolic and/or pulmonary artery wedge pressure may occur which can be considerably reduced by phlebotomy or by nitroglycerin. On the other hand it is possible that depletion of intravascular volume in coronary patients with normal or only moderately elevated left ventricular end diastolic pressure may cause a low cardiac output and decreased coronary arterial perfusion pressure and hence worsening of myocardial ischemia.<sup>18-21</sup> Therefore

the indication of intravenous nitroglycerin in patients with coronary artery disease should be determined primarily on the basis of the systemic blood pressure and left ventricular end diastolic pressures.

### Summary

Left ventricular dynamics as well as systemic and coronary hemodynamics were determined in 14 patients with coronary artery disease (1) under control conditions, (2) under intravenous infusion of nitroglycerin, (3) under continued infusion of nitroglycerin with restored arterial and pulmonary artery pressures induced by the parallel infusion of dextran. Heart rate was kept constant by atrial pacing.

| SWI<br>[gm m/m] | HR<br>[beats/min] | TPRI<br>[mm Hg/min/L m] | PyRI<br>[mm Hg/min/L m] | v<br>[ml/min 100 g] | MVO<br>[ml/min 100 g] | Volume infused<br>[ml] |
|-----------------|-------------------|-------------------------|-------------------------|---------------------|-----------------------|------------------------|
| 49.7            |                   | 29.3                    | 4.5                     | 65                  | 7.9                   |                        |
| 47.4            | 74                | 25.7                    | 2.3                     | 57                  | 6.8                   |                        |
| 51.3            |                   | 20.8                    | 4.1                     | 65                  | 8.2                   | 500                    |
| 29.9            |                   | 31.8                    | 6.3                     | 56                  | 5.6                   |                        |
| 18.0            | 90                | 39.1                    | 5.1                     | 54                  | 5.9                   |                        |
| 38.6            |                   | 24.3                    | 5.0                     | 63                  | 6.7                   | 500                    |
| 47.7            |                   | 38.0                    | 5.4                     | 64                  | 8.8                   |                        |
| 30.3            | 72                | 37.9                    | 7.8                     | 47                  | 6.3                   |                        |
| 49.0            |                   | 37.4                    | 5.3                     | 69                  | 8.9                   | 550                    |
| 44.6            |                   | 26.6                    | 6.0                     | 87                  | 8.3                   |                        |
| 34.0            | 93                | 24.3                    | 5.3                     | 65                  | 6.4                   |                        |
| 59.5            |                   | 24.4                    | 5.3                     | 94                  | 10.7                  | 530                    |
| 4.5             |                   | 31.8                    | 5.2                     | 68                  | 7.4                   |                        |
| 33.0            | 107               | 29.1                    | 4.0                     | 59                  | 6.7                   |                        |
| 41.4            |                   | 24.7                    | 4.0                     | 97                  | 10.5                  | 540                    |
| 45.4            |                   | 38.7                    | 5.5                     | —                   | —                     |                        |
| 43.4            | 0                 | 36.4                    | 1.7                     | —                   | —                     |                        |
| 54.3            |                   | 37.9                    | 5.5                     | —                   | —                     | 400                    |
| 48.0            |                   | 38.0                    | 5.0                     | —                   | —                     |                        |
| 79.7            | 71                | 34.6                    | 1.5                     | —                   | —                     |                        |
| 60.6            |                   | 26.3                    | 4.1                     | —                   | —                     | 400                    |
| 44.6            | 80                | 33.0                    | 5.6                     | 66                  | 7.7                   |                        |
| ± 9.6           | ± 11              | ± 4.2                   | ± 0.8                   | ± 9.6               | ± 1.2                 |                        |
| 33.8            | 80                | 31.9                    | 4.0                     | 57                  | 6.5                   |                        |
| ± 9.9           |                   | ± 6.5                   | ± 1.6                   | ± 9.3               | ± 1.2                 |                        |
| <0.001          |                   | NS                      | <0.001                  | <0.001              | <0.001                |                        |
| ~30%            |                   | ~3%                     | ~29%                    | ~13%                | ~15%                  |                        |
| 53.7            | 80                | 28.4                    | 5.0                     | 85                  | 9.3                   | 437                    |
| ± 7             |                   | ± 4.7                   | ± 0.9                   | ± 2%                | ± 1.6                 | ± 128                  |
| NS              |                   | <0.001                  | <0.005                  | <0.01               | <0.005                |                        |
| +10%            |                   | ~14%                    | ~1%                     | +98%                | +21%                  |                        |

Intravenous nitroglycerin infusion resulted in a significant reduction in left ventricular systolic (20 per cent) and end diastolic pressure (43 per cent) peak dp/dt (13 per cent) cardiac index (16 per cent) stroke volume index (15 per cent) and stroke work index (30 per cent). Peak (dp/dt/total pressure) increased (15 per cent). Pulmonary vascular resistance markedly decreased (29 per cent) whereas total peripheral resistance did not change significantly (~3 per cent). Both coronary blood flow of the left ventricle (13 per cent) and myocardial oxygen consumption (15 per cent) decreased parallel to the reduction in preload and afterload. The action of nitroglycerin at restored left ventricular and pulmonary artery pressures was characterized by increase in peak

dp/dt (12 per cent) peak (dp/dt total pressure) (18 per cent) cardiac index (13 per cent) stroke volume index (14 per cent) and stroke work index (10 per cent). Both coronary blood flow (28 per cent) and myocardial oxygen consumption (21 per cent) increased parallel to the enhancement of ventricular performance.

The results demonstrate that intravenous nitroglycerin produces effective diastolic and systolic unloading of the heart associated with reduction in myocardial oxygen consumption and in coronary blood flow. There was marked vascular pooling which quantitatively averaged  $437 \pm 128$  ml. This occurred concomitant with a 43 per cent decrease in left ventricular end diastolic pressure or a 20 per cent decrease in peak

systolic pressure. Significant coronary dilating properties of nitroglycerin could not be detected in these coronary patients. The increase in left ventricular contractility indices at restored pressure suggests a moderate but significant positive inotropic effect of nitroglycerin.

# REFERENCES

- Brachfeld N, Bozer J and Gorlin R. Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects. *Circulation* 19:697, 1959.
- Brachfeld N. Coronary vasomotor response to pharmacologic agents. *Am J Cardiol* 13:1, 1964.
- Ferrer M I, Bradley S E, Wheeler H D, Enson Y, Preisig R, Bruckner F W, Conroy R J and Harvey R M. Some effects of nitroglycerin upon the splanchnic pulmonary and systemic circulation. *Circulation* 33:357, 1966.
- Mason D T and Braunwald E. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 32:755, 1965.
- Strauer B E, Westberg C and Tauchert M. Untersuchungen über inotrope Nitroglycerinwirkungen am isolierten Ventrikelmyokard. *Pflügers Arch (Eur J Physiol)* 324:124, 1971.
- Strauer B E. Evidence for a positive inotropic effect of nitroglycerol and the isolated human ventricular myocardium. *Pharmacol Res Commun* 3:377, 1971.
- Dumesnil J G, Ritman F L, Davis G D, Gau G T, Rutherford H D and Frue F L. Regional left ventricular wall dynamics before and after sublingual administration of nitroglycerin. *Am J Cardiol* 36:419, 1975.
- Greenberg H, Dwyer E M, Jameson A G and Pinkernell B M. Effects of nitroglycerin on the major determinants of myocardial oxygen consumption. *Am J Cardiol* 36:426, 1975.
- McAnulty J H, Hattenhauer M T, Rosch J, Kloster F E and Rahmtoola S M. Improvement in left ventricular wall motion following nitroglycerin. *Circulation* 51:140, 1975.
- Honig C R, Tenney M and Gabel P V. The mechanism of cardiovascular action of nitroglycerin. An example of integrated response during the unsteady state. *Am J Med* 29:910, 1960.
- Declaration of Helsinki—Recommendations guiding doctors in clinical research. *J Clin Invest* 46:1140, 1967.
- Warner H R and Wood E H. Simplified calculation of cardiac output from dye dilution curves recorded by oximeter. *J Appl Physiol* 5:111, 1952.
- Zimmerman H A. Intravascular catheterization. Springfield 1972. Charles C Thomas Publisher.
- Bretschneider H J, Cott J, Hilgert G, Probst R and Rau G. Gaschromatographische Trennung und Analyse von Argon als Basis einer neuen Fremdgasmethode zur Durchblutungsmessung von Organen. *Verh Dtsch Ges Kreislaufforsch* 32:267, 1966.
- Rau G. Messungen der Koronardurchblutung mit der Argon Fremdgasmethode. *Arch Kreislaufforsch* 58:322, 1969.
- Strauer B F, Brune J, Schenk H, Knoll D and Perings E. Lupus cardiomyopathy: cardiac mechanics, hemodynamics and coronary blood flow in uncomplicated systemic lupus erythematosus. *Am Heart J* 92:715, 1976.
- Tauchert M. Koronarreserve und myokardiale Sauerstoffverbrauch des menschlichen Herzens. *Basic Res Cardiol* 58:183, 1973.
- Graham T P, Covell J W, Ross J Jr, Sonnenblick E H and Braunwald E. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. *J Clin Invest* 47:310, 1968.
- Lee S J, K Sung Y K and Zaragoza A J. Effects of nitroglycerin on left ventricular volumes and wall tension in patients with ischemic heart disease. *Br Heart J* 32:790, 1970.
- Sonnenblick E H and Ross J Jr, Braunwald E. Oxygen consumption of the heart: Newer concepts of its multifactorial determination. *Am J Cardiol* 22:325, 1968.
- Fowler N O, Bloom W L and Ward J A. Hemodynamic effects of hypervolemia with and without anemia. *Circ Res* 6:163, 1958.
- Fowler N O and Holmes J C. Dextran-induced anemia and reduction on blood viscosity in the heart lung preparation. *Am Heart J* 68:204, 1964.
- Gowdey C W. Cardiac output and acute experimental methemoglobinemia. *Can J Biochem Physiol* 38:1411, 1960.
- Khajia F, Sanghvi V, Mark A and Parker J O. Effect of volume expansion on the angina threshold. *Circulation* 43:824, 1971.
- Murray J F, Escobar E and Rapaport E. Effect of blood viscosity on hemodynamic responses in acute normovolemic anemia. *Am J Physiol* 216:638, 1969.
- Greene H L, Kelly D T, Taylor D R and Pitt B. Hemodynamic effect of plasma volume expansion and prognostic implications in acute myocardial infarction. *Circulation* 49:106, 1974.
- Peterson K L, Skloven D, Ludbrook P, Uther J B and Ross J Jr. Comparison of isovolumic and ejection phase indices of myocardial performance in man. *Circulation* 49:1088, 1974.
- Müller O and Rörvik K. Hemodynamic consequences of coronary heart disease. With observations during anginal pain and on the effect of nitroglycerine. *Br Heart J* 20:312, 1959.
- Needleman P. Organic nitrates. Berlin Heidelberg New York 1970. Springer Verlag.
- Wiener L, Dwyer E M and Cox J W. Hemodynamic effects of nitroglycerin, propranolol and their combination in coronary heart disease. *Circulation* 39:673, 1969.
- Strauer B E. Dynamik Koronardurchblutung und Sauerstoffverbrauch des normalen und kranken Herzens. Basel, München, Paris, London, New York, Sydney 1975. S. Karger AG.
- Amende I, Simon R and Lichtlen P R. Effects of beta blockade and nitroglycerin on diastolic pressure-volume relation in patients with coronary artery disease. *Circulation* 54 (Suppl II):2-5, 1976.
- Ludbrook P A, Byrne J D, Kumik P B and McNaught R C. Consistent left ventricular diastolic compliance despite altered loading conditions in response to nitroglycerin. *Circulation* 55 (Suppl II):596, 1966.
- Strauer B E. Force-velocity relations of isotonic relaxation in mammalian heart muscle. *Am J Physiol* 224:431, 1973.
- Gorlin R. Drugs and angina pectoris. *Am J Cardiol* 10:419, 1962.
- Strauer B E and Scherpe A. Myocardial mechanics and oxygen consumption in experimental hyperthyroidism in the cardiac sarcoplasm. *Rec Adv Card Struct*

- Metab vol. 8 ed. P E Rosi and P Harris Baltimore 1975 University Park Press pp 49-502.
- 37 Strauer B E, Beer H, Heitlinger K, and Höfling B Left ventricular systolic wall stress as a primary determinant of myocardial oxygen consumption. Comparative studies in patients with normal left ventricular function with pressure and volume overload and with coronary heart disease. *Basic Res Cardiol* 72:306 1977
- 38 Strauer B E, Heitlinger K, and Burger S Coronary hemodynamics and myocardial oxygen consumption in essential hypertension. *Circulation* 56 (Suppl. III) III 81R 1977 (Abstr.)
- 39 Gold H H, Leinbach R C, and Sanders C A Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction. *Circulation* 46:839 1972
- 40 Hershfield J W, Borer J S, Goldstein R E, Barrett M J., and Epstein S E Reduction in severity and extent of myocardial infarction when nitroglycerin and methoxamine are administered during coronary occlusion. *Circulation* 49:291 1974
- 41 Smith, F. H, Redwood, D R., McCarron W E., and Epstein S E Coronary artery occlusion in the conscious dog. Effects of alterations in arterial pressure produced by nitroglycerin hemorrhage and alpha-adrenergic agonists on the degree of myocardial ischemia. *Circulation* 47:51 1973

# Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material."

# The difference vector Assessment of effects of changes or interventions

Clifford V Nelson, Ph D  
Brian C Hodgkin Ph D  
R Alan Bonner, D V M , Ph D  
Evangelos T Angelakos, M D , Ph D  
Portland Me

In studying the electrocardiographic changes after any procedure or disease, one usually looks at alterations in waveform amplitude duration, or vector direction. We wish to discuss another approach, i.e., the vector which represents the difference between the postoperative and preoperative vectors. The vectorcardiogram (VCG) is the resultant of all the forces occurring during the electrical activity of the heart. At a given instant of time large areas may be excited simultaneously. If the change affects only a portion of the heart there may be normal spread over parts of the heart as well as spread through the injured portion resulting in an abnormal resultant vector.

Bayley<sup>1</sup> referred to the dead zone vector which summates with the normal vector in cases of infarction. He pointed out that this vector exists only during progress of accession over regions of the myocardium containing the dead tissue. If one assumes that excitation is normal in unaffected tissue then the difference between post infarction and pre infarction vectors should be due entirely to the abnormal excitation. This approach has been used by Flowers and colleagues<sup>2,3</sup> in constructing difference surface potential maps.

From the Maine Medical Center Portland and the Biomedical Research Institute University of Maine at Portland/Gorham Portland Maine

This research was done under Contract NIH 71 2495 and Research Career Award K6-HL-1932 (CYN) from the National Institutes of Health Department of Health Education and Welfare

Received for publication June 27 1977

Accepted for publication July 5 1977

Reprint requests C V Nelson Ph D Maine Medical Center Portland ME 04107

## Digression on vectors

Although the properties of vectors are discussed in standard textbooks we wish to point out a few aspects of the difference vector as an aid in understanding the results. In Fig 1A the vector difference between vectors T and U is a vector U-T drawn between the tips of T and U. Without loss of generality vector U-T can be transferred to the origin.

In Fig 1B vector T has increased to vector U without change in direction. Vector U-T lies along the same axis. If T decreased in magnitude U-T would lie along the same axis but point in the opposite direction (Fig 1C). Fig 1D shows that the difference vector U-T can be larger than either vectors T or U. The magnitude (as well as the direction) of the difference between two vectors depends, therefore, both on the magnitudes of the original vectors and the angle between them.

## Methods

Infarcts or ischemic areas were produced in young pigs (6 to 12 weeks old) by ligating the left anterior descending coronary artery (LADA) or one of its branches. VCGs were obtained before and one to two weeks after surgery using the lead system previously described.<sup>4</sup> Upon termination, the heart was excised, sectioned, and weighed. The location and extent of the infarcts were determined at this time.

Vector spatial magnitudes and directions were found by applying X, Y, and Z signals to an analog computer. The difference vectors were calculated for the postoperative and preoperative peaks of the spatial magnitude (M) curves.

Curves of  $M$ ,  $M_1$ , and  $M_2$  were plotted for preoperative and postoperative cases. At each instant of time we computed

$$M_E = M_2 - M_1$$

$$M_{1D} = M_2 - M_{11}$$

$$M_D = M_2 - M_1$$

Here  $M_D$  is the difference between postoperative and preoperative values of  $M$  at a given instant of time etc.  $M_1$  is then the  $\lambda$  component of the difference vector  $M_1$ ,  $M_D$ ,  $H_D$ , and  $V_D^\circ$ , are found as before and are given by

$$M_1 = \sqrt{M_E^2 + M_{1D}^2 + M_D^2}$$

$$H_D = \tan^{-1} \left( \frac{M_1}{M_D} \right)$$

$$V_D^\circ = \sin^{-1} \left( \frac{M_{1D}}{M_D} \right)$$

## Results

The  $M$  curves had one to three peaks. These peaks were designated  $M_1$ ,  $M$  and  $M_2$  and corresponded to excitation of septum, ventricular free walls and basal portions of ventricles and septum. Since the experimental animal was the young growing pig and since dipole moment depends on heart size, difference vectors were computed for a normal pig over a two week period (Fig. 2). It is seen that there was little change in vector direction during this time.

In another animal (pig No. 13) the LADA was ligated high up above the branches. The heart fibrillated but was brought back by electric shock treatment. There was a large infarct in the wall of the left ventricle extending nearly to the apex. The infarcted area was 1.6 by 2.0 cm and was 3.5 mm thick. The LV wall thickness was 7.4 mm. Fig. 3 shows preoperative, postoperative and difference vectors for the  $M$ ,  $M_1$  and  $M_2$  peaks. The small  $M$  control vector pointed to right anterior (ventrad) and up (cephalad). One week after the ligation  $M$  shifted to the right but still upwards. The  $M$  difference vector  $D$  pointed to right posterior and up (Fig. 3). The LADA supplies the anterior wall and septum including about one third of the RV and anterior and lateral portion of the LV free wall and apex. The position of the  $D$  vector could be due to an infarcted region of the anterior portion of the septum causing the vector to point towards the right posterior rather than anteriorly.

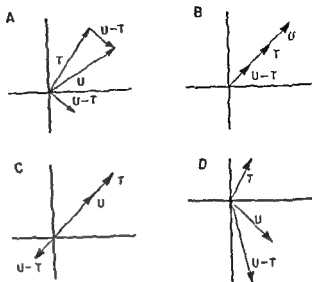


Fig. 1. Diagrams showing two vectors  $T$  and  $U$  and the difference vector  $U-T$  (see text for explanation).

The  $M_1$  vector pointed initially to left posterior and down. The seven day postoperative vector shifted in a counterclockwise (ccw) direction so that it pointed nearly directly posteriorly and down. The difference vector  $D$  however pointed to the right slightly posterior and up. This is consistent with the presence of an infarct on the anterior wall of the heart.

The  $M_1$  vector initially directed towards the left posterior and upwards also shifted ccw. The difference vector  $D_1$  was close to  $D$  in position. Vectors  $D$ ,  $D_1$  and  $D_2$  should represent the effect of the infarction better than the postoperative vectors alone.

Pig No. 35 had no  $M_1$  peak but changes in the  $M_1$  and  $M_2$  peaks were very similar to those for pig No. 13. In pig No. 35 the LADA was ligated about one third of the way down from the base just above the apical branch. There were ischemic zones on the septum facing the left ventricle ( $1.5 \times 1 \times 0.2$  cm) on the apical endocardium ( $0.25$  cm thick) and on the LV middle endocardium ( $3 \times 2 \times 0.15$  cm). With this extensive involvement it is not surprising that both  $M_1$  and  $M_2$  vectors were altered.

In pig No. 51 (Fig. 4) a region of the right ventricle (RV) was also infarcted. The  $M_1$  vector initially to the right anterior and horizontal shifted after infarction to left anterior and upwards (Fig. 4). The difference vector  $D$  was also in this direction. In this animal the tie was located half way between base and apex on the

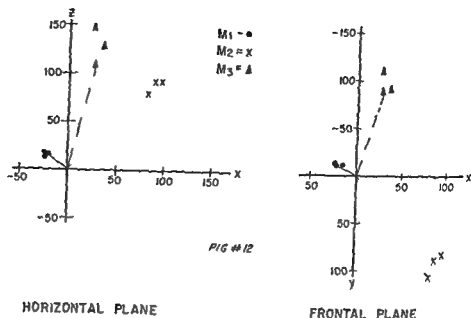


Fig 2 Effects of two weeks growth on horizontal and frontal plane vectors of a normal pig. Initial age was six weeks. Lines are drawn for the initial vectors only. Difference vectors were very small and are not shown. In all diagrams +X is to left, +Y down (caudad) and +Z posterior.

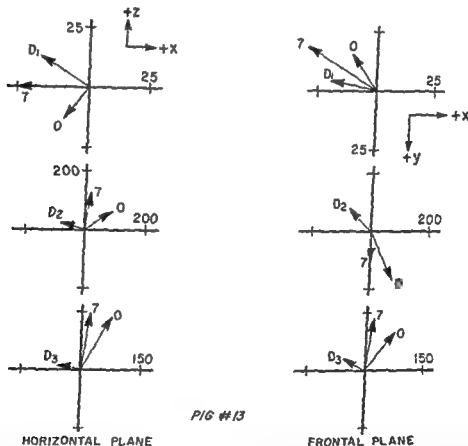


Fig 3 M, M<sub>1</sub>, and M<sub>2</sub> peak vectors for pig No 13 with transmural infarct on wall of left ventricle. Vectors are preoperative (zero days) postoperative (7 days) and the difference vectors (D). Note differences in scales.

LADA: Infarction was found on the RV (3.5 × 0.25 × 0.25 cm) the septum (3 × 1.5 × 0.4 cm) the apex (2.8 × 1.2 × 0.5 cm) and the LV free wall (2.3 × 2.3 × 0.3 cm). Changes in the M<sub>1</sub> vector (Fig 4) were similar to those for pig No 13 (Fig 3) except that D<sub>1</sub> was to

the right anterior and slightly down instead of to the right posterior and somewhat up. The fact that D<sub>1</sub> pointed to the left away from the RV may have been caused by the RV involvement.

Fig 5 shows M control post ligation and difference vectors for two pigs which had infarcts

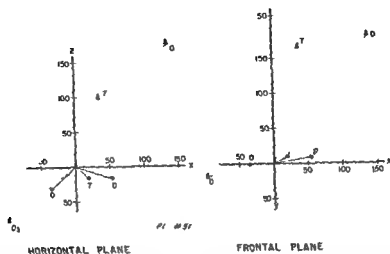


Fig 4 M and M peak vectors for pig No 51 There was an infarct on the right ventricle as well as on the septum apex and LV The initial difference vector D points towards the left away from the infarcted right ventricle

extending into the septum apex and LV anterior free wall Pig No 32 had the largest infarct involving 38.0 Gm of the LV free wall The control vector pointed to the right anterior and down Eight days after the ligation the vector had shifted to left posterior and down with the difference vector left posterior and up Pig No 33 had an infarct in the same general location but the septum was somewhat more involved than the LV free wall or apex The zero and seven day vectors pointed to left posterior and down but the difference vector was left posterior and up Even though the control vectors for the two pigs had quite different directions the difference vectors were in the same spatial octant M occurs at about the time of the rapid shift of the normal vector from anterior to posterior so that control vectors can be either anterior or posterior For 17 control pigs the mean H° vector was -5 degrees but with a standard deviation of 76 degrees The normal V° angle for these controls was 50 degrees with SD = ± 19 degrees

In pig No 23 ligation of the left circumflex coronary artery produced a small (1.75 Gm) infarct in the base of the LV The control M<sub>p</sub> vector pointed to left posterior and up Seven days after the ligation the vector shifted to nearly directly posterior and up The difference vector however was to the right and upwards

Because most of the pigs did not have all three M<sub>p</sub>, M<sub>s</sub> and M<sub>i</sub> peaks we also examined the difference vector during the entire QRS complex Fig 6 shows curves of M<sub>p</sub>, H° and V° during QRS for pig No 51 which is the same animal as in Fig

4 Fig 6A shows that the normal M curve had two peaks M<sub>p</sub> and M<sub>s</sub> Seven days after ligation of the LADA the curve had changed significantly The M<sub>p</sub> peak was no longer evident The dipole moment increased between 15 and 40 per cent of QRS duration (PQD) and an M<sub>i</sub> peak appeared From 40 to 80 PQD M decreased M<sub>s</sub> dropped by nearly one third Since this pig had infarcted areas in RV septum LV and apex there were changes throughout most of QRS

Fig 6A also shows the difference vector magnitude curve This is not generally equal to the algebraic differences between the other two curves It is seen that M<sub>p</sub> has peaks at about 25 and 55 PQD The peak at 25 PQD is due to the infarcts in RV and septum The later peak would correspond to infarct in the apex and IV

Fig 6B shows curves of the horizontal angle H° during QRS The preoperative H° curve is normal i.e. the horizontal plane vector swings from right anterior to left anterior and then left posterior The post ligation curve is somewhat similar except that the swing from anterior to posterior is more gradual The difference H° curve however shows that the horizontal difference vector pointed to the left posterior until 35 PQD and then swung rapidly to the right anterior It then stayed in the right anterior but with a movement towards left anterior at about 70 PQD Up to 35 PQD M<sub>p</sub> pointed away from the RV and septum The later anterior direction was caused by the infarcts in the LV and apex and possibly also a change in the excitation pathway

Fig 6C shows the variation of the vertical



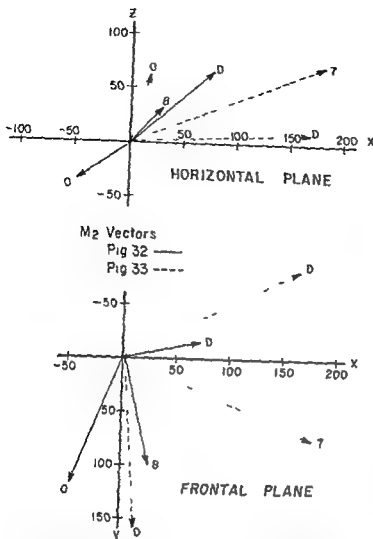


Fig 5 M peak vectors for pigs No 32 (solid lines) and pig No 33 (broken lines). Although the control vectors were nearly oppositely directed in the horizontal plane the difference vectors had a similar orientation.

angle,  $V^\circ$ . The preoperative curve was again normal showing an initial superior direction followed by inferior between 18 and 43 PQD. After this time the direction was superior again. The postoperative  $V^\circ$  curve was similar in shape but was displaced in a superior direction. The maximum downward angle with the horizontal plane was 35 degrees instead of 85 degrees. The  $V^\circ$  curve of the difference vector did not resemble either the normal or postoperative curve but had two positive (downward) peaks and two negative (upward) peaks. The first peak of  $M_p$  at 27 PQD pointed to the left horizontal and somewhat posterior. The second peak at 54 PQD corresponding fairly closely with  $M_1$  pointed to right anterior and downwards nearly opposite to the normal  $M_1$  direction.

Another example of the usefulness of the difference vector is shown in Fig 7. The data were

taken from Table III of a previous publication on the changes in spatial dipole moment after surgical repair of atrial septal defect. It was found that the M peak, corresponding to excitation of ventricular free walls increased after the shunt was repaired. The explanation was offered that the RV vector was increased by the larger blood volume in this ventricle. This opposed the LV vector, resulting in a smaller resultant vector. A problem was that after surgery, with the diminution of the RV vector, one would expect the magnitude to increase but with a leftward shift of the resultant vector, instead of the rightward shift which was found. Fig 7 shows a possible explanation of this apparent inconsistency. The reason lies in the direction of the difference vector which represents the effect of the increased blood in the right ventricle. This vector points to right posterior instead of right anterior as one might assume. If the difference vector had pointed to the right anterior, there would have been a leftward shift of the postoperative vector. In the case of secundum atrial septal defect, the postoperative vector may be considered more nearly normal than the preoperative vector because normal blood volumes are restored. Thus we believe the original explanation was correct and the rightward shift was due to the abnormal RV vector.

## Discussion

Vectorcardiographic diagnosis of infarction is based on the concept that the dead tissue contributes no voltage to the resultant vector which consequently tends to point away from the site of the infarction. If the infarct is small or involves only a limited portion of the myocardium, the dead zone vector summates with the vector due to excitation of normal myocardium and only partially points away from the inactive tissue.

In Fig 4 the  $M_1$  vector shifted from right anterior to left anterior seven days after ligation of the LADA. The difference vector points somewhat more to the left but in this case the seven day vector is fairly close to the difference vector. The  $M_1$  difference vector is pointed in an entirely different direction from the  $M_1$  seven day vector, however. The  $M_1$  seven day vector is shifted towards left posterior and upwards so that a diagnosis of an inferior location of the infarct

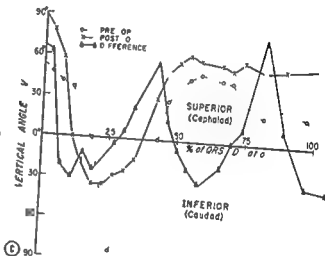
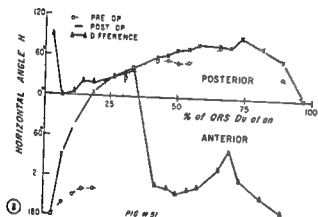
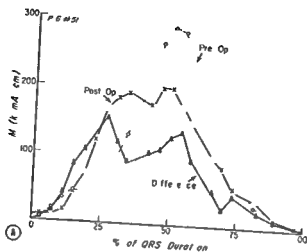


Fig 6 Curves of  $M_H$  and  $V$  during QRS for pig No 51. The curves show control values, seven days after ligation of the LADA and differences vectors

Fig 6 The curves show control values, seven days after ligation of the LADA and differences vectors

might be made. The D vector points towards right anterior and down more in keeping with the actual location of the injured tissue.

We have studied primarily the effects of infarcts on the three spatial magnitude dipole moment peaks. These peaks are however representative of the heart's excitation since they occur during excitation of septum and right ventricle free walls of both ventricles and late basal excitation of LV and septum. The location and extent of the infarction determines which peaks are affected. An infarct in RV alone would involve  $M$  and  $M$  peaks whereas a transmural infarct in the LV might affect both  $M$  and  $M$  peaks.

Whether or not excitation is normal in uninjured areas of the heart would depend on indirect effects of the infarct such as altered hemodynam-

ics contractility etc. Up to the time the excitation wave reaches the affected region the spread should be normal. After reaching the infarcted tissue however it is possible that new wavefronts might be established or the time sequence of excitation might be altered so that an abnormal terminal pattern might result. Intra infarction excitation waves may follow circuitous routes resulting in large time differences in local excitation. Therefore late ECG patterns may be abnormal even though the infarct involved regions of the heart energized earlier.

A complicating factor is that the pig heart excitation is different from other species such as the human, dog, or monkey. Hamlin and associates studied excitation of the minipig heart which has a QRS duration of about 80 msec. The young pigs used in our study had a mean QRS

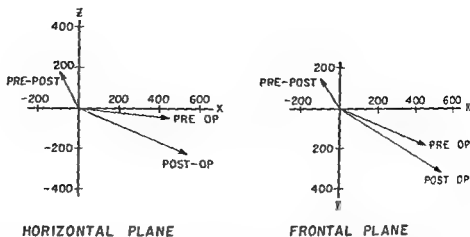


Fig 7 Change in vectors after surgical correction of secundum atrial septal defect. Data are from Reference No 7. The difference vector represents the effect of the increased volume of blood in the right ventricle.

duration of 40.5 msec. We have assumed that the excitation is similar to that for the adult minipig heart and have expressed times as percentage of QRS duration in order to compare results.

There are four stages in the pig heart excitation. From zero to 13 to 19 PQD, the apical third of septum is excited from left to right and also from right to left. There would probably also be some spread along the axis of the septum. This would result in three vectors, the largest directed towards right anterior and upwards, a smaller oppositely directed vector and a third small vector towards left/right posterior and upwards. An infarct in the left ventricular side of the septum would eliminate or reduce the left to right forces so that the smaller right to left forces would predominate, producing a vector to the left posterior. This might explain the early changes shown in Fig 6.

The next stage consists of excitation of RV in a direction downwards to the left anterior and a smaller LV wave front in the opposite direction. There is also excitation of the septum in an apex to base direction. The larger RV force is opposed by the LV and septal forces so that the net voltage is not too large. This stage is from about 15 to 40 PQD. An RV infarct would reduce the RV force so that the net vector would instead be pointed upwards to left and posterior. In Fig 6 at 25 PQD the normal vector pointed to the right anterior and downwards. The difference vector at this time is directed towards the left posterior and only slightly downwards. The postoperative vector increased because of less cancellation and the difference vector magnitude was large.

The third stage (40 to 75 PQD) consisted of rapid spread through the remaining ventricular

walls and continued apex to base septal excitation. The normal vector is pointed up posterior and either left or right (Fig 6). Basal portions of both ventricles are excited at this time. During the final stage activation of the basal septum is completed. Fig 6 shows that the difference vectors from 40 to 75 PQD were nearly opposite the normal vectors as they were directed toward right anterior and down. This might be caused by an infarct in the septum or on the caudal portion of the anterior wall which is activated rather late. The earlier abnormal spread might in part cause the abnormal activation at this time.

The position of the pig heart within the thorax is similar to the heart's position in the dog. The RV lies above and to the right of the septum. The septum makes an angle of about 30 degrees with the vertical axis (head-foot) and 45 degrees with the transverse plane. The heart tilts forward from dorsad to ventrad with the apex near the anterior wall.

One would expect that with the tangential and oppositely directed excitation of the ventricles the VCG would be quite different from that of the dog or human being. All of our controls however showed H° and V° curves during QRS which closely resembled such curves for dogs and human beings. The main difference was that the M<sub>z</sub> vector was largest in the pig whereas in the dog and human being M<sub>x</sub> is the largest peak.

The lowered M<sub>z</sub> vector in the pig might be due to the effects of intracardiac blood which enhanced voltages due to radial spread and attenuated voltages due to tangential spread. This does not explain why the H° and V° curves are so similar in all three species however.

## Summary

Vector dipole moments were measured on young pigs before and one week after ligation of the left anterior descending coronary artery. Vectors were obtained for the three peaks of vector spatial magnitude M. Preoperative postoperative and difference vectors were measured for each peak. If excitation is normal except through the infarcted tissue the difference vector should be more closely related to the infarct because the normal excitation cancels out. It was found that the postoperative vector was changed by the infarct but that the difference vector was a better indication of infarction. This paper was designed to introduce the method using experimental data for a small number of pigs.

## REFERENCES

1. Bayliss H H. Biophysical principles of electrocardiography. New York 1958. Paul H Hoeber Inc.
2. Flowers, N C, Horan L G, and Johnson J C. New evidence for infero posterior myocardial infarction on surface potential maps. Am J Cardiol 38:376 1976.
3. Flowers, N C, Horan L G, and Johnson J C. Anterior infarctional changes occurring during mid and late ventricular activation detectable by surface mapping techniques. Circulation 54:906 1976.
4. Nelson C V, Gastonguay P R, Wilkinson A F, and Voukydis P C. A lead system for direction and magnitude of the heart vector in Vectorcardiography 2. Hoffman I, Hamby R I, and Glassman E, eds. Amsterdam 1971. North Holland Publishing Company p 85.
5. Hodgkin H C, Nelson C V, and Angelakos E T. Magnitude, direction and location of the resultant dipole moment of the pig heart. J Electrocardiol 9:123 1976.
6. Nelson C V, Hodgkin H C, and Gastonguay P R. Dipole moment of the hearts of various species. Ann Biomed Eng 3:308 1975.
7. Nelson C V, Dowling J T, and Sloman G. Changes in heart dipole moment after surgical correction of atrial septal defect. Am HEART J 81:766 1976.
8. Durrer D, Van Lier A A W, and Buiter J. Epicardial and intramural excitation in chronic myocardial infarction. Am HEART J 68:65 1964.
9. Hamlin R L, Burton R R, Leverett S D, and Burns J W. Ventricular activation process in minipigs. J Electrocardiol 8:113 1975.
10. Hamlin R L. The QRS electrocardiogram, epicardio-gram, vectorcardiogram and ventricular excitation of swine. Am J Physiol 198:37 1960.
11. Nelson C V, Rand P W, Angelakos E T, and Hugenholz P. Effect of intracardiac blood on the spatial vectorcardiogram. Part I. Results in the dog. Circ Res 31:95 1972.
12. Hodgkin H C, Millard, R W, and Nelson C V. Effect of hematocrit on electrocardiographic potentials and dipole moment of the pig. Am J Physiol 232:H406 1977.

# Effects of proximal intra-atrial Wenckebach on distal atrioventricular nodal, and His-Purkinje, block

With special reference to the theory of alternating Wenckebach periods

Agustin Castellanos, MD  
Ruey J. Sung, MD  
Stephen M. Mallon, MD  
Martin G. Bloom, MD  
Robert J. Myerburg, MD  
Miami, Fla

Most reports discussing alternating Wenckebach periods (AW) have referred to its occurrence in a single structure, generally the atrioventricular (A-V) node<sup>1</sup> and less frequently the His-Purkinje system.<sup>2-4</sup> There have been only a few published examples of AW resulting from simultaneous involvement of two different structures which in the reported cases have been the two mentioned above.<sup>5-7</sup> Therefore the purpose of this communication is to discuss the effects that a proximal intra-atrial Wenckebach type of conduction disturbance can have on higher degrees of block occurring in more distally located structures, placing special emphasis on the general theory of AW and of multilevel block.

## Material and methods

Electrophysiological studies were performed in eight patients after explaining the procedure and obtaining informed consent. Drugs had been discontinued for at least 48 hours. His bundle electrograms were obtained as previously outlined with a tripolar catheter electrode placed across the tricuspid valve.<sup>8</sup> A hexapolar catheter electrode was also introduced through an antecubital

vein to record or pace from the high right atrium, mid right atrium and right ventricular apex. In six patients stimulation from high right atrium (at a distance of approximately 15 to 25 mm from the high right atrial electrode pair of the hexapolar catheter) was performed through a third catheter electrode, which in the early phase of the study had been placed inside the coronary sinus. Interelectrode distance was 10 mm. The programmed stimulator used delivered rectangular pulses of 2 msec duration and approximately twice diastolic threshold values.

As in other laboratories part of the workup of our patients with recurrent supraventricular tachyarrhythmias includes attempts to induce A-V reciprocating tachycardias as well as atrial flutter or fibrillation.<sup>9-11</sup> This was attempted on two separate occasions in each patient by gradually increasing the pacing rate up to 300/minute.

This report deals with the events occurring when these attempts resulted in a pattern suggestive of intra-atrial Wenckebach as defined below.

## Definitions

HRA and MRA were the high right atrial and mid right atrial deflections recorded by the corresponding electrode pairs of the hexapolar catheter.

LRA was the low right atrial deflection in the His bundle electrographic (HBE) lead. It was the pacemaker stimulus artefact

From the Division of Cardiology, Department of Medicine, University of Miami School of Medicine and the Cardiovascular Section, Jackson Memorial Hospital, Miami, Fla.

Received for publication July 5, 1977.

Accepted for publication Aug. 19, 1977.

Reprint requests: Agustin Castellanos, MD, Division of Cardiology, University of Miami School of Medicine, P.O. Box 530875, Miami, Fla. 33152.

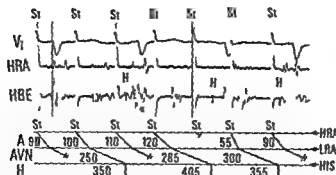


Fig 1 (Case 3) 2:1 St H block with coexisting proximal intra atrial Wenckebach and distal 2:1 A V nodal (LRA H) block. Completion of the proximal Wenckebach cycle in the stimulus (fifth from the beginning of the strip) which was blocked (at the distal level) during the 2:1 St H sequence prevented the appearance of 3:1 St H block. St = pacemaker stimulus artefact delivered to the high right atrium through the quadripolar catheter electrode. HRA = high right atrial electrogram recorded by the hexapolar catheter electrode. LRA = low septal right atrial electrogram recorded from the vicinity of the A V node (AVN) in the His bundle electrographic (HBE) lead. A = atria, H = His bundle. Numbers at the A, AVN (astrovventricular nodal) and H level indicate duration of St LRA, LRA, H and St H intervals respectively. In this and all following figures values are expressed in msec.

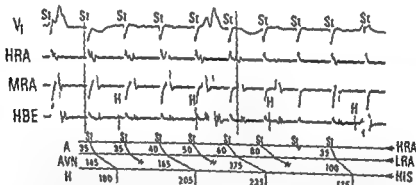


Fig 2 (Case 6) 2:1 St H block with coexisting proximal intra atrial Wenckebach and distal 2:1 A V nodal (LRA H) block. Completion of the proximal intra atrial Wenckebach cycle in the stimulus which was conducted during the 2:1 sequence resulted in progression to 3:1 St H block.

The St LRA interval was used as a rough measurement of intra atrial conduction time (from paced HRA site to the vicinity of the A V node).

The LRA H and H V intervals were used to estimate A V nodal conduction time and His Purkinje conduction time respectively.

The St H interval represented the conduction time through the atria (proximal level) and the A V node (distal level).

The St V interval included conduction time through the atria (proximal level), A V node (distal level) and His Purkinje system (distal level).

An intra atrial Wenckebach was an episode of progressive prolongation of St LRA intervals until one stimulus was not followed by a propagated response.

A completed AW period<sup>12</sup> was an episode of 2:1 St H (or St V) block in which there was a prolongation in transmission intervals of conducted beats ending with two or three consecutive stimuli failing to reach the His bundle (or ventricles) that is with conversion of 2:1 into 3:1 or 4:1 St H (or St V) block.

An abortive AW period was an episode of 2:1 St H (or St V) block in which the progressive prolongation in transmission intervals of conducted beats was interrupted or changed before progression into 3:1 block had time to occur.

## Results

In all patients intra atrial Wenckebach occurred at cycle lengths (210 to 275 msec) which were shorter than those at which 2:1 LRA H block had occurred (280 to 350 msec). When

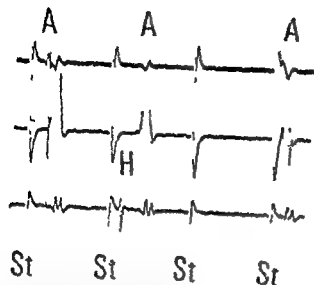


Fig 3 (Case 6) Enlargement of the part of Fig 2 which showed that the prolongation of the corresponding stimulus to response intervals occurred between the pacing site and closest recording electrodes. From top to bottom: high right atrial, mid right atrial, and low right atrial electrograms.

HRA pacing was performed 15 to 25 mm from the closest (also HRA) recording electrodes. It was observed that the gradual increase in the stimulus response intervals occurred between pacing site and recording HRA electrodes (Figs 1 to 4). Therefore the time elapsing between inscription of HRA and MRA electrograms and between MRA and LRA electrograms was the same at all St St intervals.

Six patients developed intra atrial Wenckebach during 2:1 St H block resulting from 2:1 A V nodal (LRA H) block (Table I). In four cases the stimulus which was not followed by a LRA deflection was that which had been blocked at the A V node (LRA electrogram not followed by H deflection) during the 2:1 sequence (Table I and Fig 1). Therefore, conversion to 3:1 block did not occur.

Fig 1 also shows that while the intra atrial Wenckebach was occurring (at a pacing cycle length of 270 msec) there also was a gradual prolongation of St H intervals (abortive AW) manifested by an increase of St H intervals from 350 to 405 msec. This abortive AW (due to delays at both, atrial and A V nodal levels) was modified by the completion of the intra atrial Wenckebach since the latter decreased the St H intervals from 405 to 355 msec.

In two patients (Cases 5 and 6) the intra atrial Wenckebach ended with the stimulus which had been able to traverse the A V node during the 2:1 sequence (LRA deflection followed by H electro-

gram). This resulted in progression to 3:1 St H block.

Fig 2 depicts an AW of St H interval (ending in two consecutively blocked stimuli) due to the coexistence of proximal (intra atrial) Wenckebach (manifested by a gradual increase of St LRA intervals) with distal (A V nodal) abortive AW (manifested by prolongation of LRA H intervals during 2:1 LRA H block). This occurred while the pacing cycle length was decreased from 235 to 210 msec.

In three patients the intra atrial Wenckebach appeared when the overall conduction pattern was that of 4:1 St V block (Table II). In one of the two patients with distal 4:1 A V nodal (LRA H) block (Case 7) the intra atrial Wenckebach was completed in a stimulus which would have been blocked (thereby maintaining the 4:1 ratio) but in Case 8 it terminated in the stimulus which would have been conducted. The latter resulted in progression to 5:1 St H block (Fig 4) due to the documented existence of conduction disturbances in two different structures (atrial proximal, and A V node distal).

In one case the 4:1 St V block occurred because of alternation of 2:1 A V nodal (LRA H) block with 2:1 His Purkinje (H V) block (Fig 5). The intra atrial Wenckebach was completed in the stimulus which would have been conducted (when the pacing cycle length had been reduced from 250 msec to 220 msec) thereby resulting in progression into 5:1 St V block. This was due to the documented existence of block in three different structures (atria, proximal, A V node distal and His Purkinje, distal).

## Discussion

**Mechanisms of gradual prolongation of St LRA electrograms.** The interval between a stimulus delivered through a catheter electrode and an electrogram recorded by another catheter electrode comprises the time required for the local response to attain a sufficient intensity to allow propagation and the conduction time to the recording electrodes.<sup>22</sup> The farther the electrodes the greater the contribution of conduction time.

In the six patients in whom HRA pacing was performed relatively close to the recording HRA electrodes the progressive delay in stimulus-response intervals occurred in the vicinity of the stimulated site (Figs 1 to 4). Hence the propor-

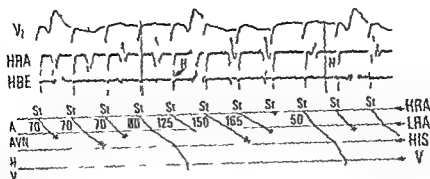


Fig 4 (Case 7) Proximal intra atrial Wenckebach during 4:1 St V block due to 4:1 A V nodal LRA H block. Completion of proximal Wenckebach cycle in a stimulus which could have conducted results in progression to 5:1 St V block. Although only two levels of conduction impairment could be documented (atria and A V node) conventional electrocardiographic theory suggested a third (intra nodal) level. However the existence of the latter could not be proved even with His bundle recordings.

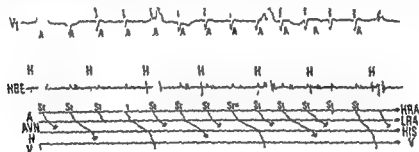


Fig 5 (Case 5) Proximal intra atrial Wenckebach during 4:1 St V block due to alternation of 2:1 A V nodal (LRA H) and 2:1 His-Purkinje (H V) block. Completion of the proximal Wenckebach cycle in the stimulus which was conducted during the 4:1 sequence produced a progression in the degree of block (to 5:1). The latter resulted from documented three level block involving three separate structures (atria, A V node and His Purkinje system).

tion with which true latency and slowed conduction around the pacing electrode contributed to the genesis of the intra atrial Wenckebach could not be determined with certainty.<sup>1</sup> However in other cases with intra atrial disease the prolongation of the St LRA electrograms has occurred after the inscription of the HRA electrogram that is between the latter and the LRA electrogram.

Because this phenomenon occurs within the atria several authors have suggested that the term intra atrial Wenckebach pattern can be applied from a descriptive point of view regardless as to its exact electrophysiological mechanism.

A similar prolongation of stimulus to response intervals was observed in canine hearts by Lewis and associates<sup>2</sup> during stimulation of the muscle in the vicinity of the superior vena cava.

In one experiment (their Fig 8) the tracing showed an increase of the stimulus to response intervals (from 37 to 140 msec) before the development of 2:1 block at a pacing rate of 370/minute.<sup>21</sup>

Drury<sup>1</sup> noted that the stimulus to response intervals were longer during 2:1 intra atrial block than when 1:1 conduction occurred when the rate was one half. A similar phenomenon is known to occur at the A V node.<sup>1</sup> Both have been attributed to the (concealed) intra atrial or A V nodal conduction of the apparently blocked stimulus.<sup>22</sup>

Some authors have described Wenckebach or AW patterns presumably occurring in the atrial myocardium surrounding ectopic foci or pacing electrodes during spontaneous automatic atrial tachycardias and rapid atrial stimulation.<sup>2, 23</sup>

Patterns resulting from the occurrence of



Table 1 Clinical and electrophysiological information in patients developing intra atrial Wenckebach during 2 1 St H block (due to 2 1 A V nodal, or LRA H, block)

| Case | Age | Diagnosis | St LRA (control) | LRA H (control) | CL of 2 1 LRA H block | CL of IAW | Maximal St LRA | IAW completed in | Consecutively blocked St | Conversion 2 1 into 3 1 block |
|------|-----|-----------|------------------|-----------------|-----------------------|-----------|----------------|------------------|--------------------------|-------------------------------|
| 1    | 53  | RSVT      | 45               | 95              | 280                   | 225       | 115            | Blocked St       | 1                        | No                            |
| 2    | 49  | RSVT      | 60               | 115             | 370                   | 270       | 120            | Blocked St       | 1                        | No                            |
| 3    | 67  | RSVT      | 55               | 75              | 350                   | 275       | 120            | Blocked St       | 1                        | No                            |
|      |     | PCSD      |                  |                 |                       |           |                |                  |                          |                               |
| 4    | 56  | SSS       | 60               | 85              | 345                   | 230       | 125            | Blocked St       | 1                        | No                            |
| 5    | 73  | PCSD      | 55               | 105             | 305                   | 215       | 105            | Conducted        | 2                        | Yes                           |
| 6    | 62  | WPW       | 35               | 100             | 280                   | 210       | 80             | Conducted        | 2                        | Yes                           |
|      |     | PCSD      |                  |                 |                       |           |                |                  |                          |                               |
|      |     | RSVT      |                  |                 |                       |           |                |                  |                          |                               |

RSVT = repetitive supra-ventricular tachyarrhythmia PCSD = primary conducting system disease SSS = sick sinus syndrome WPW = Wolff Parkinson White syndrome St = stimulus artifact LRA = low right atrium H = His bundle CL = cycle length IAW = intra atrial Wenckebach

Table II Clinical and electrophysiological information in patients developing intra atrial Wenckebach during 4 1 St V block

| Case | Age | Diagnosis | St LRA control | LRA H control | CL of 4 1 St V block | Type of 4 1 St V block             | CL of IAW | Maximal St LRA | Consecutive very blocked St | IAW completed in |
|------|-----|-----------|----------------|---------------|----------------------|------------------------------------|-----------|----------------|-----------------------------|------------------|
| 7    | ■   | PCSD      | 55             | 115           | 230-260              | 4 1 LRA H                          | 225       | 115            | 4                           | Blocked St       |
|      |     | RSVT      |                |               |                      |                                    |           |                |                             |                  |
| 8    | 59  | PCSD      | 75             | 95            | 240-260              | 4 1 LRA H                          | 210       | 165            | 5                           | Conducted St     |
|      |     | SSS       |                |               |                      |                                    |           |                |                             |                  |
| 6*   | 62  | WPW       | 55             | 100           |                      | 2 1 LRA H alternating with 2 1 H V | 210       | 80             | 0                           | Conducted St     |
|      |     | PCSD      |                |               |                      |                                    |           |                |                             |                  |
|      |     | RSVT      |                |               |                      |                                    |           |                |                             |                  |

Abbreviations as in Table I

Same patient as in Table I but different attempt to induce atrial flutter or fibrillation

**intra atrial Wenckebach during A V nodal (LRA H) 2 1 block** Although Halpern and colleagues<sup>7</sup> consider that AW can be due to a single level of block most authors accept that it is due to two levels of block occurring generally in one structure.<sup>1, 8, 11, 13</sup>

Even with His bundle recordings the limits of the proximal and distal levels can only be surmised when AW occurs exclusively at the A V node (manifested by the corresponding variations of the LRA H intervals) or exclusively at the His Purkinje system (manifested by the expected changes of the H V intervals).<sup>7, 9, 13</sup>

In three previously reported cases of AW resulting from two levels of block occurring in two separate structures, the A V node and the His Purkinje system were involved but not the atria.<sup>7, 11, 13, 20</sup> These studies as well as the present communication support the two level block

concept since the limits of the proximal and distal levels could be determined by the intracardiac electrograms.

It is generally accepted that AW ending with two blocked impulses is due to the association of proximal Wenckebach with distal (fixed) 2 1 block.<sup>7, 9</sup> However Fig 2 shows that AW of St H intervals can also result from the coexistence of proximal and distal Wenckebach or AW cycles.

Although this mechanism had not been proved with His bundle recordings, Kosowsky and colleagues implied (using only the surface electrocardiogram) that Wenckebach cycles can be simultaneously present in both proximal and distal A V nodal levels. In fact the ladder diagram below Fig 8 of the article by Kosowsky and colleagues depicts proximal 5 4 and 6 5 Wenckebach associated with distal 4 3 Wenckebach.<sup>9</sup>

Patterns resulting from the occurrence of

**intra atrial Wenckebach during 4:1 St V block**  
This study shows that a proximal intra atrial Wenckebach can occur during 4:1 St V block without increasing the degree of block provided that the cycle was completed in stimuli which would have been blocked during the 4:1 sequence. However conversion of 4:1 into 5:1 did occur when the Wenckebach cycle ended within the stimuli which would have been conducted (Figs 4 and 5).

In the two patients in whom the 4:1 St V block was due to 4:1 A V nodal (LRA H) block (Fig 4) two levels of conduction impairment were demonstrated (atria and A V node respectively). In conventional electrocardiographic interpretations it is usually accepted that 4:1 A V nodal block can result from a two level block, the upper level stopping every other impulse and the lower level stopping every other one which traversed the upper region.<sup>1</sup> If this concept is correct the events depicted in Fig 4 can be attributed to a three level conduction disturbance involving two separate structures.

Moreover 5:1 A V nodal block has been attributed to three level conduction disturbance.<sup>1</sup> This assumption is supported by the findings in Fig 5 where 4:1 St V block (due to alternation of 2:1 A V nodal block and 2:1 His Purkinje block) progressed into 5:1 St V block when the intra atrial Wenckebach was completed in the stimulus which would have been conducted.

**Clinical implications** A great number of assumptions used in present day electrocardiographic interpretation were originally made by deductive reasoning from clinical tracings. Many have been corroborated by extrapolating information obtained from recording action potentials from the various components of the conducting system and by directly recording His bundle activity in man in conjunction with artificial pacing of atria and ventricles.<sup>12</sup>

As mentioned previously the existence of multilevel block has been used for many years to explain a variety of commonly encountered arrhythmias.

Although the exact incidence of multilevel block at the A V node has not been determined with certainty Kosowsky and colleagues postulated that it could occur more often than suspected since they were able to identify 36 cases during a two year period in a 415 bed general community hospital.<sup>6</sup> Kosowsky

and colleagues considered it as a frequent usually transient conduction pattern which by itself had no short term detrimental prognostic implications. On the other hand multilevel block at the His Purkinje system carries a bad prognosis insofar as A V conduction is concerned.<sup>1</sup>

It is thus evident that validation of the theory of AW (a manifestation of multilevel block) has a direct bearing on the diagnosis, treatment and electrocardiographic recognition of commonly encountered arrhythmias.

## Summary

Intra atrial Wenckebach patterns of stimulus to response intervals coexisting with distal A V nodal and His Purkinje blocks occurred in eight patients during high right atrial stimulation at rapid rates. In two patients with 2:1 St H block and in two patients with 4:1 St V block an increase in the degree of block occurred when the proximal intra atrial Wenckebach cycle was completed with the stimulus which otherwise would have been propagated to the distal levels. However the degree of block did not increase when the intra atrial Wenckebach terminated in distally blocked stimuli. In one patient progression of 4:1 into 5:1 St V block was due to the association of intra atrial Wenckebach with alternating 2:1 block at the A V nodal and His Purkinje levels.

Contrasting with most reports dealing with the mechanisms of alternating Wenckebach in a single structure this study permitted the determination of the boundaries between proximal and more distal levels. It also showed that alternating Wenckebach cycles (of St H intervals) ending with two consecutively blocked stimuli could result from the association of proximal intra atrial Wenckebach with distal A V nodal Wenckebach or abortive AW cycles.

The electrophysiology of documented two or three level block in different structures has validated previously made assumptions regarding multilevel block in a single structure.

## REFERENCES

1. Katz L. N. and Pick, A. Clinical electrocardiography Part 1. The arrhythmias. Philadelphia 1966 Lea & Febiger pp 413-418.
2. Beccam Santander M. Pick A. and Langendorf R. A V conduction in auricular flutter. Circulation 2 604 1960.
3. Parkinson, J. and Bedford D. T. The course and

- treatment of auricular flutter Q J Med 21 21 1977
- 4 McMillan T M and Bellet J Auricular Flutter Some of its clinical manifestations and its treatment based on the study of sixty five cases Am J Med Sci 184 331 1932
  - 5 Hartzler G O and Maloney H D Supra His alternate beat Wenckebach dysrhythmia Mayo Clin Proc 50 475 1975
  - 6 Kosovsky H D Latif P and Radoff A M Multilevel atrioventricular block Circulation 54 914 1976
  - 7 Amat y Leon F Chuquimia R Wu D, Denes P Dhingra, R C Wyndham C and Rosen K M Alternating Wenckebach periodicity A common electro physiologic response Am J Cardiol 36 757 1975
  - 8 Schamroth L The disorders of cardiac rhythm Oxford 1971 Blackwell Scientific Publications pp 303 407
  - 9 Halpern M S Nau G J Levi R J Elizar M V and Rosenbaum M B Wenckebach periods of alternate beats Clinical and experimental observations Circulation 48 41 1973
  - 10 Schullens R M and Durrer D Conduction disturbances located within the His bundle Circulation 45 612 1972
  - 11 Touboul P Clement Ch Delahaye J P and Gonin A Etude de la conduction auriculo ventriculaire dans les arhythmies supraventriculaires à l'aide des enregistrements du potentiel du faisceau de His Arch Mal Coeur 64 190 1971
  - 12 Cohen H C D Cruz I and Pick A Concealed intra ventricular conduction in the His bundle electrogram Circulation 53 776 1976
  - 13 Brusca A Rosettani E Mangiardi, L Bonamini, R., and Orzan F Atypical second degree A V block due to bilateral bundle branch block with Wenckebach phenomenon and concealed conduction in the bundle branch system Eur J Cardiol 5 183 1977
  - 14 Agha A S Befeler B Castellanos A M Sung R J Castillo C A Myerburg R J and Castellanos A Bipolar catheter electrograms for study of retrograde atrial activation pattern in patients without pre excitation syndromes Br Heart J 38 641 1976
  - 15 Sellers T D Jr Campbell R W F Bashore T M and Gallagher J T Effects of procaine amide and quinidine supplement in the Wolf Parkinson White syndrome Circulation 55 15 1977
  - 16 Wellens H J J The electrophysiological properties of the accessory pathway in the Wolf Parkinson White syndrome in The Conduction system of the heart Structure function and clinical implications Wellens H J J Lie K I and Janse M I eds Leiden 1976 HE Stenfert Kroese BV pg 567 587
  - 17 Castellanos A Jr Iyengar H Agha A S and Castillo C A Wenckebach phenomenon within the atria Br Heart J 34 1121 1972
  - 18 Krikler D M and Goodwin J F. Cardiac arrhythmias Philadelphia 1975 W B Saunders Company p 12
  - 19 Narula O S Runge M and Sarret P Second degree Wenckebach type A V block due to block within the atrium Br Heart J 34 1127 1972
  - 20 Puech P Grolleau R Cabasson J Baisus C and Latour H Blocs auriculo-ventriculaire du premier et deuxième degré par trouble de conduction intra auriculaire Arch Mal Coeur 68 19 1975
  - 21 Mullar R N S Maurer B J Reid D S Wray R, Burkhead J S and Shillingford J P Studies of intra atrial conduction with bipolar atrial and His bundle electrograms Br Heart J 35 604 1973
  - 22 Brooks C McC Hoffman B F Suckling E E., and Oras O Excitability of the Heart New York 1966 Grune & Stratton Inc p 80
  - 23 Castellanos A Sung R J, Aldrich J L Mendoza J J and Myerburg R J Alternating Wenckebach periods occurring in the atrium His Purkinje system Wenckebach and Kent bundle Am J Cardiol (in press)
  - 24 Lewis, T Fell H S and Stroud W M Observations on flutter and fibrillation Part III Some effects of rhythmic stimulation of the auricles Heart 7 241 1918
  - 25 Drury A N Further observations upon intrasauricular block produced by pressure or cooling Heart 12 143 1925
  - 26 Lewis T and Master A M Observations upon conduction in the mammalian heart Heart 12 209 1925
  - 27 Langendorf R Pick A Edelst A and Katz L N Experimental demonstration of concealed AV conduction in the human heart Circulation 27 386 1963
  - 28 Langendorf R Concealed A V conduction The effect of blocked impulses on the formation and conduction of subsequent impulses AM HEART J 35 547 1945
  - 29 Schamroth L The theory and mechanism of the Wenckebach phenomenon S Afr Med J 4 827 196
  - 30 Castillo C Maytin O and Castellanos A Jr His bundle recordings in atypical A V nodal Wenckebach block during cardiac pacing Am J Cardiol 27 50 1971
  - 31 Langendorf R and Pick A Concealed conduction Further aspects of propagation of the cardiac impulse Circulation 13 381 1956
  - 32 Langendorf R Newer aspects of concealed conduction of the cardiac impulse The conduction system of the heart Structure function and clinical implications. Editors Wellens H J J Lie K I and Janse M J ed Leiden 1976 HE Stenfert Kroese BV pp 410-413
  - 33 Watanabe Y and Dreifus L S Levels of concealment in second degree and advanced A V block In Cardiac arrhythmias edited by Dreifus L S and Likoff W New York 1973 Grune & Stratton Inc p 303

### Misdiagnosis of atrial septal defect in patients with hereditary telangiectasia (Osler-Weber-Rendu disease) and hepatic arteriovenous fistulas

Wallace E Radtke MD  
Hugh C Smith MD  
Richard E Fulton MD  
Martin A Adson MD FACS  
Rochester, Minn

High output congestive heart failure secondary to arteriovenous malformations is a well recognized entity. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) is known to be associated with arteriovenous fistulas particularly of the lung. Much less common is a hepatic arteriovenous malformation in combination with this disease. When such an uncommon malformation occurs it seldom produces a hyperkinetic circulation.

We wish to describe two patients who had Osler-Weber-Rendu disease and large hepatic arteriovenous malformations. Initially both patients had signs and symptoms of congestive heart failure that were believed to be due to atrial septal defects and both underwent cardiac catheterization and exploratory cardiectomy.

#### Case report

**Case 1.** A 46-year-old white woman was first seen at the Mayo Clinic on October 28, 1971. Her chief complaints were exertional dyspnea, occasional paroxysmal nocturnal dyspnea, and anginal chest pains. At the age of 17 years she had been told of a heart murmur but she had no history of acute rheumatic fever or congenital heart disease. She had multiple hemangiomas of the lips and tongue for many years with occasional episodes of bleeding. She had experienced an episode of hematemesis in 1959 and had had several transfusions.

On examination her blood pressure was 124/60 mm Hg

with a regular pulse of 92 beats per minute. Multiple telangiectatic lesions on the lips and tongue were noted. Her precordium was hyperactive with the cardiac apex 2 to 3 cm to the left of the midclavicular line in the fifth intercostal space. A Grade 5/6 holosystolic murmur was heard loudest at the left sternal border but it was widely transmitted over the entire thorax and to the neck. The second heart sound split normally and there was no diastolic murmur. A presystolic gallop was recorded. Also noted was an enlarged nonpulsating liver.

The hemoglobin level was 6.8 Gm/dl with a normal leukocyte count. A platelet count was 563,000/mm<sup>3</sup> with a reticulocyte count of 1.7 per cent. The sedimentation rate was 44 mm in 1 hour. The serum iron level was 33 µg/dl (9 per cent saturation) and a blood smear demonstrated changes consistent with chronic blood loss. Fluoroscopic views of the heart showed cardiac enlargement with mild biventricular enlargement and enlargement of the left atrium. There was an increase in the intensity of the aortic pulsations both in the ascending and the descending aorta. Electrocardiogram revealed a rate of 90 beats per minute with sinus arrhythmia and voltage criteria for left ventricular hypertrophy. The following were normal: urinalysis, haptoglobin levels, stools for occult blood, test of renal function, and a roentgenogram of the stomach.

While hospitalized the patient was transfused with packed red blood cells and her hemoglobin level increased to 11.2 Gm/dl. Results of cardiovascular examination were unchanged despite the increase in hemoglobin concentration. Clinically the loss of blood was considered to be due to bleeding from hemangiomas within the gastrointestinal tract. Because of the uncertain cardiac diagnosis and her primary complaints she underwent cardiac catheterization on November 4, 1971.

Double-dye sampling (Fig. 1) and hemodynamic data and oxygen saturations (Table 1) suggested a large left-to-right shunt presumed to be at atrial level. Abnormal pressure elevations (Table 1) consistent with long-standing left-to-right shunting and volume overload were observed. However the clinical findings did not entirely support the findings of atrial

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Received for publication Dec. 8, 1976.

Accepted for publication Jan. 7, 1977.

Reprint requests: Dr. W. E. Radtke, Mayo Clinic, 3 Broadway Street, N. E., 55905.

- treatment of auricular flutter *Q J Med* 21 21 1977
- 4 McMillan T M and Bellet, J. Auricular Flutter: Some of its clinical manifestations and its treatment based on the study of sixty five cases *Am J Med Sci* 184 331 1932
  - 5 Hartzler G O and Maloney H D. Supra His alternate beat Wenckebach dysrhythmia *Mayo Clin Proc* 50 476 1975
  - 6 Kosowsky M D, Latif P and Radoff A M. Multilevel atrioventricular block *Circulation* 54 914, 1976
  - 7 Amat, J, Leon F, Chuquimia H, Wu D, Denes P, Dhingra R C, Wyndham C., and Rosen K M. Alternating Wenckebach periodicity: A common electro physiologic response *Am J Cardiol* 36 757 1975
  - 8 Schamroth L. The disorders of cardiac rhythm Oxford 1971 Blackwell Scientific Publications pp 303 407
  - 9 Halpern M S, Nau G J, Levi R J, Elzari M V, and Rosenbaum M B. Wenckebach periods of alternate beats: Clinical and experimental observations *Circulation* 48 41 1973
  - 10 Schulenburg R M and Durrer D. Conduction disturbances located within the His bundle *Circulation* 45 612 1972
  - 11 Touboul P, Clement Ch, Delahaye J P and Gonin A. Etude de la conduction auriculo ventriculaire dans les arythmies supraventriculaires à l'aide des enregistrements du potentiel du faisceau de His *Arch Mal Coeur* 64 190 1971
  - 12 Cohen H C, D Cruz I and Pick A. Concealed intra ventricular conduction in the His bundle electrogram *Circulation* 53 776 1976
  - 13 Brucce A, Rosettani E, Mangardi L, Bonamini R., and Orzan F. Atypical second degree A V block due to bilateral bundle branch block with Wenckebach phenomenon and concealed conduction in the bundle branch system *Eur J Cardiol* 5 183 1977
  - 14 Agha A S, Befefer B, Castellanos A M, Sung R J, Castillo C A, Myerburg R J and Castellanos A. Bipolar catheter electrograms for study of retrograde atrial activation pattern in patients without pre excitation syndromes *Br Heart J* 38 641 1976
  - 15 Sellers T D Jr, Campbell R W F, Bashore T M, and Gallagher T T. Effects of procaine amide and quinidine supplement in the Wolf Parkinson White syndrome *Circulation* 55 15 1977
  - 16 Wellens H J J. The electrophysiological properties of the accessory pathway in the Wolf Parkinson White syndrome in The Conduction system of the heart: Structure function and clinical implications. Wellens H J J, Lie K I and Janse M I eda. Leiden 1976 HE Stenfert Kroese BV pp 567 587
  - 17 Castellanos A Jr, Iyengar R, Agha A S and Castillo C A. Wenckebach phenomenon within the atria *Br Heart J* 34 1121 1972
  - 18 Kinkler D M and Goodwin J F. Cardiac arrhythmias. Philadelphia 1975 W B Saunders Company p 12
  - 19 Narula O S, Runge M and Samet, P. Second degree Wenckebach type A V block due to block within the atrium *Br Heart J* 34 1127 1972
  - 20 Puech P, Grolleau R, Cabasson J, Bassus C and Latour H. Blocs auriculo ventriculaire du premier et deuxième degré par trouble de conduction intra auriculaire *Arch Mal Coeur* 68 19 1975
  - 21 Millar R N S, Maurer B J, Reid D S, Wn R, Burkhead J S and Shillingford J P. Studies of intra atrial conduction with bipolar atrial and His bundle electrograms *Br Heart J* 35 604 1973
  - 22 Brooks C, McC Hoffman H F, Suckling E E and Onas O. Excitability of the Heart New York 1958 Grune & Stratton Inc p 80
  - 23 Castellanos A, Sung R J, Aldrich J L, Merdoza J J and Myerburg R J. Alternating Wenckebach periods occurring in the atrium His Purkinje system Wenckebach and Kent bundle *Am J Cardiol* (in press)
  - 24 Lewis T, Fell H S and Stroud W H. Observations on flutter and fibrillation Part III. Some effects of rhythmic stimulation of the auricles *Heart* 7 47 18 6 1920
  - 25 Drury A N. Further observations upon intrasutricular block produced by pressure or cooling *Heart* 12 144 1925
  - 26 Lewis T and Master, A M. Observations upon conduction in the mammalian heart *Heart* 12 209 1925
  - 27 Langendorf R, Pick A, Edelstein A and Katz L N. Experimental demonstration of concealed AV conduction in the human heart *Circulation* 27 386 1963
  - 28 Langendorf R. Concealed A V conduction: The effect of blocked impulses on the formation and conduction of subsequent impulses *AM HEART J* 35 547 1949
  - 29 Schamroth L. The theory and mechanism of the Wenckebach phenomenon *S Afr Med J* 4 877 1967
  - 30 Castillo C, Maytin O and Castellanos A Jr. His bundle recordings in atypical A V nodal Wenckebach block during cardiac pacing *Am J Cardiol* 27 5 1971
  - 31 Langendorf R and Pick A. Concealed conduction: Further aspects of propagation of the cardiac impulse *Circulation* 13 381 1956
  - 32 Langendorf R. Newer aspects of concealed conduction of the cardiac impulse: The conduction system of the heart: Structure function and clinical implications. Editors Wellens H J J, Lie K I and Janse M J eds. Leiden 1976 HE Stenfert Kroese BV pp 410-413
  - 33 Watanabe Y and Dreifus L S. Levels of concealment in second degree and advanced A V block. In Cardiac arrhythmias edited by Dreifus L S and Likoff W., New York 1973 Grune & Stratton Inc p 205



Fig 2A (Case 1) Preoperative hepatic angiogram. Selective common hepatic injection demonstrates very large right and left hepatic arteries with high volume flow.

Postoperatively careful examination revealed a bruise over the liver. On December 16, 1971, selective hepatic and superior mesenteric arteriograms revealed a large vascular anomaly in the right and left lobes of the liver (Fig 2) along with arteriovenous malformations in the duodenum.

The patient returned to our clinic in January with severe limitation in activity and progression of exertional dyspnea, orthopnea, and ankle edema.

On February 10, 1972, the hepatic artery was ligated proximal to its gastroduodenal branch. Flow through the right hepatic artery determined by electromagnetic flowmeter was 2,350 ml/min before ligation with a reduction to 400 ml/min after ligation. Flow in the hepatic artery proximal to its bifurcation was 4,000 ml/min before ligation and diminished to 1,000 ml/min after ligation. Hemodynamic studies (Table 1) along with postoperative superior mesenteric and celiac axis arteriograms (Fig 3) performed on March 9, 1972, showed a considerable reduction in the left to right shunt. The patient was dismissed from the hospital on March 19, 1972.

**Case 2.** A 37-year-old white woman was first seen at the Mayo Clinic on August 6, 1975. Her primary complaints included recurrent nausea and vomiting associated with a low grade fever and a decrease in hemoglobin concentration to below normal. The symptoms had their onset in July 1974. Repeated attempts to localize a site of bleeding were unsuccessful.

At the age of 7 years, the patient was severely anemic and she retained a mild persistent iron-deficiency anemia most of her adult life despite regular iron therapy. Her father had hereditary hemorrhagic telangiectasia with numerous bleeding episodes from the nose and gastrointestinal tract. In March, 1971, she was noted to have cardiomegaly and a diagnosis of suspected congenital heart disease was made. In June 1974, she underwent cardiovascular evaluation because of persistent cardiomegaly, exertional dyspnea, and nonradiating chest pain. Examination at that time revealed a



Fig 2B (Case 1) Two and one half seconds after Fig 2A was made the hepatic vein (arrows) can be visualized because of rapid intrahepatic shunting.



Fig 2C (Case 1) Preoperative hepatic angiogram made 4.5 seconds after Fig 2A. Right and left hepatic veins are easily identified.

bounding heart with a Grade 2/6 murmur heard best at the upper left sternal border. Findings were reported to be consistent with aortic stenosis. The electrocardiogram showed evidence of left ventricular hypertrophy and the chest roentgenogram showed changes consistent with a large left to right shunt.

Cardiac catheterization on June 6, 1974, demonstrated a superior vena cava oxygen saturation of 74 per cent, right atrial, right ventricular, and pulmonary artery saturation of 87 per cent, and systemic arterial saturation of 95 per cent. Intracardiac pressures were normal. The findings were consis-

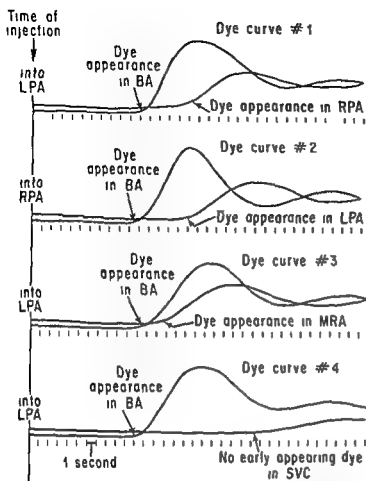


Fig 1 (Case 1) Preoperative dye curves. Selected dye curves with indocyanine green injections into right and left pulmonary arteries and sampling at central and peripheral sites. No sampling was done at level of inferior vena cava. **Dye curve 1** When dye was injected into left pulmonary artery (LPA) and continuous samples were taken from the brachial (BA) and right pulmonary arteries (RPA) dye appeared in RPA (arrow) too early (relative to the brachial artery curve) to be accounted for by normal recirculation. This is suggestive of left to right shunt to some systemic vein or right heart chamber upstream to pulmonary arteries. **Dye curve 2** Similar to Curve 1 except that the pulmonary artery dye injection and sampling catheters were reversed. Early dye is now seen in left pulmonary artery (LPA) excluding possibility of isolated anomalous pulmonary venous return. **Dye curve 3** With central sampling catheter withdrawn to right atrium (MRA) dye injected into left pulmonary artery (LPA) again appeared early in MRA (at arrow) indicating that the right atrium is at or still downstream to site of right to left shunt. **Dye curve 4** In contrast to Curve 3 dye injected into left pulmonary artery (LPA) did not appear early in central sampling catheter which was placed in superior vena cava (SVC). These curves demonstrate that the superior vena cava is upstream to site of left to right shunt and suggest that this shunt drains into right atrium—a pattern usually seen in atrial septal defects. A potential central site of left to right shunt was the inferior vena cava and this could have been excluded by a central sample curve obtained from this site which showed no early appearing dye. Absence of abnormally elevated oxygen saturation (which should occur with shunting of arterial blood) in the inferior vena cava below the diaphragm was considered to exclude this possibility (see Table I).

Table I Catheterization data in Case 1\*

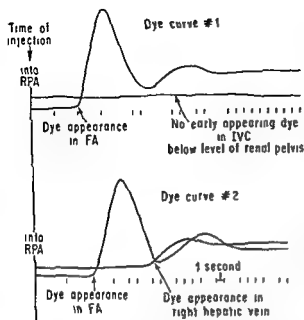
| Site                  | Preoperative<br>(Hb = 94<br>Gm./dL) |                   | Postoperative<br>(1 mo)<br>(Hb = 82<br>Gm./dL) |                   |
|-----------------------|-------------------------------------|-------------------|--|-------------------|
|                       | Pressure<br>(mm Hg)                 | Saturation<br>(%) | Pressure<br>(mm Hg)                            | Saturation<br>(%) |
| Brachial artery       | 140/72                              | 95                | 140/70   | 97                |
| Left ventricle        | 155/17 28                           | —                 | —  | —                 |
| Wedge                 | 30/21 29                            | 95                | 14/8   | 9                 |
| Pulmonary artery      | 68/30                               | 84                | 34/15  | 83                |
| Right ventricle       | 75/14                               | 83                | 39/1   | —                 |
| High right atrium     | —                                   | 72                | —  | 80                |
| Mid right atrium      | 21/10                               | 87                | 11/3   | 86                |
| Low right atrium      | —                                   | 86                | —  | 86                |
| Inferior vena cava    | —                                   | 69                | —  | 90                |
| (below diaphragm)     |                                     |                   |  |                   |
| Superior vena cava    | —                                   | 63                | —  | 79                |
| (high)                |                                     |                   |  |                   |
| Superior vena cava    | —                                   | 66                | —  | 80                |
| (low)                 |                                     |                   |  |                   |
| Calculations†         |                                     |                   |  |                   |
| Qs = 49 L/min = 31    | Qs = 95 L/min = 60                  |                   |  |                   |
| L/min/M <sup>2</sup>  | L/min/M <sup>2</sup>                |                   |  |                   |
| Qp = 11.5 L/min = 7.2 | Qp = 11.8 L/min = 7.4               |                   |  |                   |
| L/min/M <sup>2</sup>  | L/min/M <sup>2</sup>                |                   |  |                   |
| Qp/Qs = 2.3           | Qp/Qs = 1.7                         |                   |  |                   |
| Left to right         | Left to right                       |                   |  |                   |
| shunt = 60%           | shunt = 20%                         |                   |  |                   |

Note on preoperative data that both IVC and SVC O<sub>2</sub> saturation data are within normal limits but a marked increase in O<sub>2</sub> saturation occurred at level of right atrium. Preoperative saturation data are consistent with the dye dilution data suggesting left to right shunt at the atrial level. Postoperative catheterization data indicate a marked reduction in pulmonary wedge pulmonary arterial, and right ventricular pressures in addition to reduction in left to right shunt to one third of preoperative values.

†Qs = systemic flow Qp = pulmonary flow

septal defect. Moreover the early appearing central dye indicative of left to right shunt was somewhat delayed for shunting to be occurring directly across the atrial septum. Because of the patient's hereditary telangiectasia a second cardiac catheterization was performed on November 10, 1971 in an attempt to exclude the possibility of a left ventricular aortic root (sinus of Valsalva) or coronary arterial shunt to the right atrium. The left ventricular and coronary angiograms revealed no abnormalities and dye curves from the aortic root and left ventricle excluded these possibilities. Attempts to cross the septal defect were unsuccessful. Once again an oxygen saturation step up was noted at right atrial level.

The patient underwent exploratory cardiomyotomy on December 1, 1971 and complete intracardiac inspection failed to reveal any abnormality although a systolic thrill was noted over the left atrium. The surgical team noted oxygen-enriched blood returning from the inferior vena cava persistently throughout the operation and it was assumed that the left to right shunt was below the diaphragm.



**Fig 4 (Case 2)** Preoperative dye curves. Selected indocyanine green dye curves obtained at central and peripheral sampling sites (femoral artery = FA) after dye injection into right pulmonary artery (RPA). In addition to usual series of double sampling dye dilutions performed in patients with intracardiac shunts, two additional central venous sites were sampled that demonstrated subdiaphragmatic suprarenal extracardiac location of left to right shunt. **Dye curve 1:** No early appearing dye was seen in inferior vena cava (IVC) below level of renal pelvis indicating no significant left to right shunting in systemic circulation peripheral to this sampling site. **Dye curve 2:** In contrast to dye curve 1, curve 2 shows indocyanine green dye appearing too early in right hepatic vein to be accounted for by normal systemic circulation indicating a left to-right shunt upstream of hepatic vein.

was recognized as having an abdominal bruit that could have drawn attention to the presence of an intrahepatic fistula. Clinical cardiovascular examination of either patient was not entirely consistent with atrial septal defect but the combination of heart failure and a hyperdynamic circulation raised enough suspicion of a valvular or intracardiac shunt lesion that cardiac catheterization was performed. Because of the step up in oxygen saturation at the atrial level and the demonstration of left to right shunting typical of atrial septal defect by central and peripheral indocyanine green dye sampling curves it was assumed that the patients had atrial septal defect with an atypical presentation. At operation however no cardiac disease was demonstrated and because of oxygen-enriched blood returning from the inferior vena cava the strong possibility



**Fig 5A (Case 2)** Hepatic angiogram. Selective common hepatic injection preoperatively demonstrates very large right hepatic arteries with high flow.



**Fig 5B (Case 2)** Hepatic angiogram. Rapid intrahepatic shunting allows dense opacification of right hepatic veins (single arrows) and inferior vena cava (double arrowheads).





Fig 3 (Case 1) Postoperative superior mesenteric angiogram. After common hepatic ligation injection into superior mesenteric artery demonstrates reduction in size of vessels to liver with filling via pancreaticoduodenal arcade to gastroduodenal artery. There has been a considerable reduction in shunt volume.

tent with an atrial septal defect and a pulmonary flow approximately 2.6 times greater than the systemic flow.

The patient was referred for closure of the atrial septal defect and underwent exploratory cardiomy on June 21, 1974. However, no intracardiac disease was demonstrated. The surgeons reported bright red blood coming from the inferior vena cava and concluded that the left to right shunt was below the diaphragm. Later an aortogram demonstrated a massive arteriovenous fistula in the liver.

Examination at our clinic revealed a blood pressure of 110/70 mm Hg with a regular pulse of 80 beats per minute. The patient's height was 62.4 inches (158.5 cm) and weight 147 lb (66.7 Kg). She had multiple small telangiectatic lesions on the lips and tongue.

A right ventricular lift with a normal apical impulse was noted. The first and second heart sounds were normal. A prominent diastolic gallop was heard along the left sternal border. A machinery type murmur was present along the sternum with wide radiation but was most prominent over the xiphoid region and right upper quadrant.

The hemoglobin level was 12.6 Gm/dl with normal red blood cell indices, platelets and leukocyte count. Results of iron studies were also normal. The electrocardiogram showed increased QRS voltage consistent with left ventricular hypertrophy and a nonspecific T wave abnormality. A chest roentgenogram revealed cardiomegaly with increased peripheral pulmonary vascularity. Results of renal and liver function tests were normal.

Catheterization on August 18, 1975, documented the degree of left to right shunting and identified the presence of the arteriovenous malformation. A left to right shunt of 68 per cent was documented at the hepatic vein level (Table II) and selective indocyanine green dye curves confirmed the location of the shunt (Fig 4). Injection into the hepatic vessels

Table II Catheterization data in Case 2\*

| Site  | Preoperative<br>(Hb = 14.0<br>Gm/dl)         |                   | Postoperative<br>(3 wk)<br>(Hb = 19.2<br>Gm/dl) |                   |
|---|--|-------------------|---|-------------------|
|   | Pressure<br>(mm Hg)                          | Saturation<br>(%) | Pressure<br>(mm Hg)                             | Saturation<br>(%) |
| Femoral artery                                  | 146/67                                       | 94                | 110/12  | 88                |
| Pulmonary artery                                | 41/21  | 88                | 33/14   | 80                |
| Right ventricle                                 | 45/6-15                                      | 88                | —   | —                 |
| High right atrium                               | —  | 75                | —   | —                 |
| Mid right atrium                                | 13/7   | 87                | 12/6  | 81                |
| Low right atrium                                | —  | 86                | —   | —                 |
| Inferior vena cava<br>(at diaphragm)            | —  | 83                | —   | 80                |
| Inferior vena cava<br>(upper pole of<br>kidney) | —  | 73                | —   | 80                |
| Right hepatic vein                              | —  | 88                | —   | 89                |
| Superior vena cava                              | —  | 69                | —   | 73                |
| <b>Calculations†</b>                            |  |                   |   |                   |
| Qs = 3.8 L/min = 2.3<br>L/min/M <sup>2</sup>    | Qs = 7.1 L/min = 4.9<br>L/min/M <sup>2</sup> |                   |   |                   |
| Qp = 10.5 L/min = 6.2<br>L/min/M <sup>2</sup>   | Qp = 9.4 L/min = 5.5<br>L/min/M <sup>2</sup> |                   |   |                   |
| Qp/Qs = 2.7:1                                   | Qp/Qs = 1.3:1                                |                   |   |                   |
| Left to right<br>shunt = 68%                    | Left to right<br>shunt = 38%                 |                   |   |                   |

Note increased oxygen saturations in low right and mid right atrium similar to those obtained in Case 1. In this case however because of prior experience with this disease entity and the operative findings before catheterization, selective sampling from the right hepatic vein and at multiple levels in the inferior vena cava was performed. †Qs = systemic flow, Qp = pulmonary flow.

demonstrated a pronounced increase in flow with rapid arteriovenous shunting and dense filling of the hepatic veins and inferior vena cava (Fig 5).

On August 25, 1975, the common hepatic artery was ligated proximal to the gastroduodenal branch. This reduced the flow of blood determined by electromagnetic flow meter from 800 to 230 ml/min.

Postoperative catheterization on September 9, 1975, demonstrated a reduction of left to right shunting at hepatic vein level to 38 per cent (Table II). A hepatic arteriogram (Fig 5) revealed that the shunting in the liver was reduced although substantial shunting remained via collateral vessels arising from the superior mesenteric artery.

The patient was dismissed from the hospital on September 10, 1975. Eight months after operation she has remained asymptomatic and has had no recurrence of her bleeding episodes.

## Discussion

Both patients had Osler-Weber-Rendu disease. When seen initially with symptoms of heart failure and cardiac abnormalities, neither patient

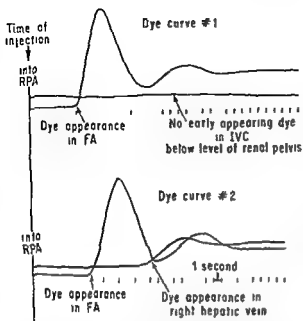


Fig 4 (Case 2) Preoperative dye curves. Selected indocyanine green dye curves obtained at central and peripheral sampling sites (femoral artery = FA) after dye injection into right pulmonary artery (RPA). In addition to usual series of double sampling dye dilutions performed in patients with intracardiac shunts two additional central venous sites were sampled that demonstrated subdiaphragmatic suprarenal extracardiac location of left to-right shunt. Dye curve 1. No early appearing dye was seen in inferior vena cava (IVC) below level of renal pelvis indicating no significant left to right shunting in systemic circulation peripheral to this sampling site. Dye curve 2. In contrast to dye curve 1, curve 2 shows indocyanine green dye appearing too early in right hepatic vein to be accounted for by normal systemic circulation indicating a left to-right shunt upstream of hepatic vein.

was recognized as having an abdominal bruit that could have drawn attention to the presence of an intrahepatic fistula. Clinical cardiovascular examination of either patient was not entirely consistent with atrial septal defect but the combination of heart failure and a hyperdynamic circulation raised enough suspicion of a valvular or intracardiac shunt lesion that cardiac catheterization was performed. Because of the step up in oxygen saturation at the atrial level and the demonstration of left to right shunting typical of atrial septal defect by central and peripheral indocyanine green dye sampling curves, it was assumed that the patients had atrial septal defect with an atypical presentation. At operation however, no cardiac disease was demonstrated and because of oxygen-enriched blood returning from the inferior vena cava, the strong possibility



Fig 5A (Case 2) Hepatic angiogram. Selective common hepatic injection preoperatively demonstrates very large right hepatic arteries with high flow.



Fig 5B (Case 2) Hepatic angiogram. Rapid intrahepatic shunting allows dense opacification of right hepatic veins (single arrows) and inferior vena cava (double arrowheads).



Fig 3 (Case 1) Postoperative superior mesenteric angiogram. After common hepatic ligation injection into superior mesenteric artery demonstrates reduction in size of vessels to liver with filling via pancreaticoduodenal arcade to gastroduodenal artery. There has been a considerable reduction in shunt volume.

tent with an atrial septal defect and a pulmonary flow approximately 2.6 times greater than the systemic flow.

The patient was referred for closure of the atrial septal defect and underwent exploratory cardiomyotomy on June 21, 1974. However, no intracardiac disease was demonstrated. The surgeons reported bright red blood coming from the inferior vena cava and concluded that the left to right shunt was below the diaphragm. Later an aortogram demonstrated a massive arteriovenous fistula in the liver.

Examination at our clinic revealed a blood pressure of 110/70 mm Hg with a regular pulse of 80 beats per minute. The patient's height was 62.4 inches (158.5 cm) and weight 147 lb (66.7 Kg). She had multiple small telangiectatic lesions on the lips and tongue.

A right ventricular lift with a normal apical impulse was noted. The first and second heart sounds were normal. A prominent diastolic gallop was heard along the left sternal border. A machinery type murmur was present along the sternum with wide radiation but was most prominent over the xiphoid region and right upper quadrant.

The hemoglobin level was 12.6 Gm/dl with normal red blood cell indices, platelets, and leukocyte count. Results of iron studies were also normal. The electrocardiogram showed increased QRS voltage consistent with left ventricular hypertrophy and a nonspecific T wave abnormality. A chest roentgenogram revealed cardiomegaly with increased peripheral pulmonary vascularity. Results of renal and liver function tests were normal.

Catheterization on August 18, 1975, documented the degree of left to right shunting and identified the presence of the arteriovenous malformation. A left to right shunt of 68 per cent was documented at the hepatic vein level (Table II) and selective indocyanine green dye curves confirmed the location of the shunt (Fig 4). Injection into the hepatic vessels

Table II Catheterization data in Case 2\*

| Site  | Preoperative<br>(Hb = 14.0<br>Gm/dL)       |                   | Postoperative<br>(Hb = 12.2<br>Gm/dL) |                   |
|---|--|-------------------|---------------------------------------|-------------------|
|   | Pressure<br>(mm Hg)                        | Saturation<br>(%) | Pressure<br>(mm Hg)                   | Saturation<br>(%) |
| Femoral artery                                  | 146/67                                     | 94                | 135/12                                | 94                |
| Pulmonary artery                                | 41/21                                      | 88                | 33/14                                 | 85                |
| Right ventricle                                 | 45/6-15                                    | 88                | —                                     | —                 |
| High right atrium                               | —  | 75                | —                                     | —                 |
| Mid right atrium                                | 13/7                                       | 87                | 12/6                                  | 84                |
| Low right atrium                                | —  | 86                | —                                     | —                 |
| Inferior vena cava<br>(at diaphragm)            | —  | 83                | —                                     | 81                |
| Inferior vena cava<br>(upper pole of<br>kidney) | —  | 73                | —                                     | 86                |
| Right hepatic vein                              | —  | 88                | —                                     | 89                |
| Superior vena cava                              | —  | 69                | —                                     | 13                |
| <b>Calculations†</b>                            |  |                   |                                       |                   |
| Qs = 38 L/min = 23<br>L/min/M <sup>2</sup>      | Qs = 71 L/min = 43<br>L/min/M <sup>2</sup> |                   |                                       |                   |
| Qp = 10.5 L/min = 62<br>L/min/M <sup>2</sup>    | Qp = 94 L/min = 55<br>L/min/M <sup>2</sup> |                   |                                       |                   |
| Qp/Qs = 2.7:1                                   | Qp/Qs = 1.3:1                              |                   |                                       |                   |
| Left to right<br>shunt = 68%                    | Left to right<br>shunt = 38%               |                   |                                       |                   |

Note increased oxygen saturations in low right and mid right atrium similar to those obtained in Case 1. In this case however because of prior experience with this disease entity and the operative findings before catheterization selective sampling from the right hepatic vein and at multiple levels in the inferior vena cava was performed.  
†Qs = systemic flow Qp = pulmonary flow

demonstrated a pronounced increase in flow with rapid arteriovenous shunting and dense filling of the hepatic veins and inferior vena cava (Fig 5).

On August 25, 1975, the common hepatic artery was ligated proximal to the gastroduodenal branch. This reduced the flow of blood determined by electromagnetic flowmeter from 800 to 230 ml/min.

Postoperative catheterization on September 9, 1975, demonstrated a reduction of left to right shunting at hepatic vein level to 38 per cent (Table II). A hepatic arteriogram (Fig 5) revealed that the shunting in the liver was reduced although substantial shunting remained via collateral vessels arising from the superior mesenteric artery.

The patient was dismissed from the hospital on September 10, 1975. Eight months after operation she has remained asymptomatic and has had no recurrence of her bleeding episodes.

## Discussion

Both patients had Osler-Weber-Rendu disease. When seen initially with symptoms of heart failure and cardiac abnormalities, neither patient

vein and superior vena cava to provide shunt localization and a second method of quantification of shunt size. Dye injected into the pulmonary artery also should be sampled in stepwise progression along the venae cavae and ideally in the hepatic vein. In our two reported cases either the omission of a central dye curve from the inferior vena cava downstream from the hepatic veins or the obtaining of an oxygen sample from the inferior vena cava upstream of the hepatic veins accounted for the failure to recognize the level of the left to right shunt at cardiac catheterization. If a surgical procedure is performed postoperative catheterization should be done to assess the effects of surgery designed to reduce the magnitude of the left to right shunt.

In 1964 Graham and associates described a patient with familial hereditary telangiectasia and hepatic artery aneurysm who had portal vein fistula. High output congestive heart failure was controlled by the surgical removal of the large shunt but the patient died of recurrent bleeding and liver failure. DeLoraine and colleagues<sup>1</sup> later reviewed the natural history of asymptomatic hepatic capillary hemangioma and emphasized the aggressive course of these lesions pointing out that most patients die from progressive heart failure. They described one patient in whom the main hepatic artery was ligated in order to diminish the large hepatic arteriovenous fistula. The patient experienced relief of heart failure and recovered. A limited number of other patients with congenital intrahepatic arteriovenous fistulas and hepatic artery portal vein fistulas have been treated by surgical means with satisfactory results. Everhart described a patient similar to our two who initially was considered to have heart failure secondary to rheumatic heart disease. Subsequent catheterization and angiography demonstrated a large hepatic arteriovenous fistula. The patient was successfully treated with ligation of the common hepatic artery.

Both of our patients underwent operation in an attempt to reduce the size of their large left to right shunts and to relieve some of the cardiac burden. Each patient had a sizable reduction in the shunt after the operation although the second patient had substantial residual shunting via collateral vessels as demonstrated by hepatic angiography.

Although at 3 and 4 weeks after operation the left to right shunting was found to be reduced

significantly in our two patients, limited experience with this problem would indicate that later recurrence of arteriovenous fistulas is probable owing to collateral arterial resupply.

### Summary

Two patients with hereditary telangiectasia (Osler Weber Rendu disease) and high output congestive heart failure secondary to large hepatic arteriovenous malformations had preoperative heart catheterization and exploratory cardiotomy to correct presumed intracardiac left to right shunts at the atrial level. At operation both patients had oxygen-enriched blood returning from the inferior vena cava. Subsequent hepatic angiography demonstrated large hepatic arteriovenous fistulas and both patients underwent hepatic artery banding and ligation with reduction of left to right shunting.

### REFERENCES

- Holman E. Abnormal arteriovenous communications peripheral and intracardiac: acquired and congenital. ed 2. Springfield Illinois 1968. Charles C Thomas Publisher.
- Hodgson C H, Burchell H M, Good C A and Claffitt O T. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula: survey of a large family. *N Engl J Med* 261:623 1959.
- Gomes M R, Bernatz P E and Dines D E. Pulmonary arteriovenous fistulas. *Ann Thorac Surg* 7:589 1969.
- Mansour K A, Hatcher C R Jr, Logan W D Jr and Abbott O A. Pulmonary arteriovenous fistula. *Am Surg* 37:263 1971.
- Graham W P III, Eiseman H and Pryor R. Hepatic artery aneurysm with portal vein fistula in a patient with familial hereditary telangiectasia. *Ann Surg* 159:362, 1964.
- Condon J R, Tanner N C and Conner D M. Hepatic artery aneurysm, hereditary haemorrhagic telangiectasia, and peptic ulceration. *Gut* 8:37 1967.
- Childers R W, Ranniger M and Rabinowitz M. Intrahepatic arteriovenous fistula with pulmonary vascular obstruction in Osler Rendu Weber disease. *Am J Med* 43:304 1967.
- Razi B, Beller B M, Ghodini J, Linhart J W, Talley R C and Urban E. Hyperdynamic circulatory state due to intrahepatic fistula in Osler Weber Rendu disease. *Am J Med* 50:809 1971.
- Burchhardt D, Stahler G A, Ludin H and Bianchi L. Hyperdynamic circulatory state due to Osler Weber Rendu disease with intrahepatic arteriovenous fistulas. *Am Heart J* 85:9 1973.
- Halpern M, Turner A F and Citron B P. Angiodysplasias of the abdominal viscera associated with hereditary hemorrhagic telangiectasia. *Am J Roentgenol* 102:783 1968.
- DeLoraine A A, Simpson E B, Baum R S and Carlson E. Hepatic artery ligation for hepatic hemangiomatous. *N Engl J Med* 277:333 1967.
- Martin L W, Benzing G and Kaplan S. Congenital



Fig 5C (Case 2) Postoperative study after ligation of common hepatic (arrow)



Fig 5D (Case 2) Hepatic angiogram. Flow is now via pancreaticoduodenal arcade (arrows)

of an arteriovenous fistula below the diaphragm was recognized.

Recently two patients with Osler Weber Rendu disease and hyperkinetic circulation secondary to intrahepatic fistula have been described.<sup>8,9</sup> Both patients had signs and symptoms of congestive heart failure as well as hepatomegaly with abdominal bruits. Chest roentgenograms revealed pulmonary plethora in both and cardiomegaly in one.<sup>8</sup> The electrocardiograms showed only repolarization changes. Each patient underwent cardiac catheterization, liver biopsy, and hepatic angiography. The liver biopsy in one



Fig 5E (Case 2) Hepatic angiogram. Superior me-ent. injection demonstrates filling of markedly reduced intrahepatic shunts via pancreaticoduodenal to gastroduodenal vessel route. Arrow denotes point of banding of gastroduodenal artery

patient was obtained during laparotomy that was performed to identify a source of recurrent bleeding. Before catheterization both patients were suspected of having extracardiac shunts. Hence a hepatic vein sample was obtained at catheterization from each patient and both patients demonstrated a marked step up in oxygen saturation at that level. One patient was treated with a cardiotonic regimen and careful clinical supervision. No remarks about treatment were made concerning the second patient.

The combination of Osler Weber Rendu disease, large intrahepatic arteriovenous malformations, and high output heart failure is rare. However, in any patient with this disease and symptoms of cardiac failure, a careful search must be made for bruits and other signs of arteriovenous fistula that may be responsible for the heart failure. Halpern and colleagues<sup>7</sup> demonstrated the useful role of angiography in delineating these lesions, particularly in the abdominal viscera. Even in the presence of an arteriovenous malformation, cardiac catheterization should be performed to determine the possible coexistence of cardiac abnormalities and to measure the magnitude of the shunt. Blood samples for oxygen saturation should be taken in stepwise fashion in the inferior vena cava, hepatic

# Pulmonary varix Report of a case with additional anomalies of the vascular pulmonary tree

C Moro  
E Marin  
A Sanchez  
J Solozabal  
Madrid Spain

Pulmonary varix is a rare benign vascular anomaly. It consists of a localized dilatation of one or more pulmonary veins that end normally in the left atrium. Its radiological appearance prompts us to rule out other similar looking disease processes such as granulomatous diseases, solitary pulmonary nodule, lung carcinoma, hilar lymph node diseases and pulmonary A-V fistula.

The first case was described by Puchet in 1843 as an autopsy finding.<sup>1</sup> The following five cases were also found in postmortem examinations. Clinically it was first diagnosed by Mouquin and associates in 1951 by means of angiography.

Until now there have been 40 published cases.<sup>1</sup> This report presents a new case with additional anomalies of the pulmonary vascular tree.

## Case report

A 21 year old female was admitted to this Hospital because of intermittent headaches. At the age of 4 years a right hilar mass was accidentally encountered. The review of systems, family and past history and physical examination were unremarkable. Laboratory examinations including ECG, EEG and skull x rays were normal. In the routine chest x ray a round mass was evident in the right hilum (Figs 1 and 2). At fluoroscopy its size and radiological density seemed to change with respiration and the Valsalva maneuver.

The suspicion of its vascular origin was ascertained by means of catheterization and right pulmonary artery angiography. Blood gas analysis and pulmonary pressures were

From the Division of Cardiology and Department of Radiology of the CS 1 de Octubre University Hospital, Madrid, Spain.  
Received for publication Dec. 8, 1976.

Accepted for publication Jan. 17, 1977.

Reprint requests: Dr. C. M. Rodríguez, Division of Cardiology, CS 1 de Octubre, Km 5.400 Carretera de Andalucía, Madrid, Spain.



Fig 1 Frontal chest x ray. A round mass is evident in the right hilum.

within normal limits. The arterial phase showed a hypoplastic right superior lobar artery (Fig 3) and the hilar mass was not opacified. However, it appeared during the venous phase simultaneously with the pulmonary veins, left atrium and ventricle and before the aorta, thus excluding any anomalous blood supply to the lung from aortic origin (Fig 4). The right superior lobar vein was absent and the dilated right inferior lobar vein corresponded exactly with the detected mass in the simple chest x ray. All these findings confirmed the diagnosis of pulmonary varix.

- intrahepatic arteriovenous fistula: report of a successfully treated case. *Ann Surg* 161:209 1965
- 13 Cohen A and De Bakky M E Successful repair of traumatic arteriovenous fistulas between hepatic artery and portal vein and right renal artery and inferior vena cava. *Surgery* 48:648 1960
- 14 Shumacker II B Jr and Waldhausen J A Intrahepatic arteriovenous fistula of hepatic artery and portal vein. *Surg Gynecol Obstet* 112:497 1961
- 15 Everhart F J An unusual cause of cardiac failure in a patient with Osler Rendu Weber disease. *St. Louis Pul Med Cent Bull* 11:73 1967

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

monary disease must be sought for Hemoptysis is an important finding that may or may not be related to the varix itself In four cases pulmonary tuberculosis and bronchiectases were associated<sup>1,2,3,4</sup> Seven other cases presented mitral valvular disease<sup>1,2,3,4,5,6,7</sup> The relation of pulmonary varix to the severity and duration of the venous hypertension is not clear since varices are rare as compared with the incidence of mitral disease On the other hand the operative treatment of the latter did not change in many cases the radiological aspect of the varix suggesting that the venous hypertension acts only as a predisposing or aggravating factor<sup>1,2,3</sup>

The reported case presented in addition to the varix a hypoplastic right superior pulmonary artery and an absent right superior pulmonary vein The venous drainage into the left atrium came through a single inferiorly located pulmonary vein Similar cases have been described by Arnett and Patton<sup>1</sup> Papamichael and colleagues<sup>2</sup> reported the association of right pulmonary varix with absence of right superior pulmonary vein and diaphragmatic eventration The association of varices with patent ductus ventricular septal defect double outlet right ventricle anomalous pulmonary venous return with pseudo coarctation of the aorta and Klippel Trenau nay Weber syndrome has also been reported<sup>3,4</sup>

The differential diagnosis includes pulmonary vascular malformations granulomatous diseases benign and malignant bronchopulmonary tumors mediastinal tumors lymph node disease processes and cysts Fluoroscopy and tomography may help to separate vascular from non vascular masses especially when the diagnosis of A-V fistula is contemplated However pulmonary angiography is the best procedure to make a diagnosis without having to recur to surgery Bartram and Strickland<sup>5</sup> in 1971 described the angiographic criteria necessary for the diagnosis of pulmonary vein varix (1) normal arterial phase of pulmonary angiography (2) opacification of the varix at the same time as the pulmonary veins (3) slow drainage into the left atrium (4) dilatation and tortuosity of the proximal vein with normal distal branches

The natural history of the pulmonary varix is not known The prognosis is good in young symptomless individuals no increase in size has been observed in several years of follow up<sup>1,2,3</sup> In

those with venous hypertension its size tends to augment<sup>1,2</sup> There are two main complications systemic embolization and fatal rupture into the pleural space or into a bronchus<sup>4,7</sup>

Regarding its treatment the cases discovered accidentally only need annual radiographic control Those related to cardiac processes may if the lesion expands be treated surgically correcting the cause of the venous hypertension and repairing the vein

#### REFERENCES

- 1 Puchet Quoted by Gumes, B. and Horvath F. Über die Vaskulitis der Pulmonalvene Fortschr. Roentgenstr. 89:54, 1958.
- 2 Hedinger E. Demonstration eines Lungenvarix. Verh. Dtsch. Ges. Pathol. 11:303, 1907.
- 3 Nauwerck D. Lungenvarix und Haemoptose. Münch. Med. Wochenschr. 70:1084, 1923.
- 4 Klinck, G. J. Jr. and Hunt H. D. Pulmonary varix with spontaneous rupture and death: report of a case. Arch. Pathol. 15:227, 1933.
- 5 Neuman B. H. Varix of pulmonary vein. Am. J. Roent. 32:608, 1934.
- 6 Jachia P. Phlebektomie im Lungenparenchym (Ein Beitrag zu den isolierten Rundschatten in der Lunge). Acta Radiol. 17:74, 1926.
- 7 Mouquin M., Hebrard H., Damasio R. et al. Varice du poulmon diagnostiqué par l'angiocardigraphie. Bull. Mem. Soc. Med. Hop. Paris 87:1091, 1951.
- 8 Bartram E. C. and Strickland B. Pulmonary varices. Br. J. Radiol. 44:974, 1971.
- 9 Kelvin F. M., Boone J. A., and Peretz D. Pulmonary varix. J. Can. Assoc. Radiol. 23:227, 1972.
- 10 Owens, D. W., Garcia E., Pierre R. R. and Castrow F. F. Klippel Trenaunay Weber syndrome with pulmonary vein varicosity. Arch. Dermatol. 108:111, 1973.
- 11 Davis J. F., Golden M. E., Prince H. L., Hastings J. E. and Chertlin H. D. Pulmonary varix: a diagnostic pitfall. Circulation 49:1011, 1974.
- 12 Ferrot W. W. and Shim M. E. Pulmonary varix. J. Thorac Cardiovasc. Surg. 68:318, 1974.
- 13 Arnett J. C. and Patton R. M. Pulmonary varix. Thorax 31:107, 1976.
- 14 Hsu I., Kehler C. A., Adkins, I. C. and Shefferman M. M. Pulmonary varix regression after mitral valve replacement. Am. J. Cardiol. 37:978, 1976.
- 15 Papamichael, M. D., Ikios D., Alkalous K. and Yanna. congenital pulmonary varicosity associated with other congenital abnormalities. Chest 62:107, 1972.
- 16 Romanoff H., Mann J. and Aviad J. Pulmonary varices. Chest 70:395, 1976.
- 17 Poller S. and Wholey M. H. Pulmonary varix evaluation by selective pulmonary angiography. Radiology 86:1078, 1966.
- 18 Hipona F. A. and Jamshidi, A. Observation on the natural history of varicosity of pulmonary veins. Circulation 35:471, 1967.
- 19 Björk, D. Dilated right pulmonary veins in mitral insufficiency. Chest 58:24, 1970.
- 20 Castleman, B., Mallory T. B. and Towne V. W. Case records of the Massachusetts General Hospital. Engl. J. Med. 245:575, 1951.
- 21 Reck G., Walther, R. and Dagher I. Bilateral pulmo-





Fig 2 Lateral chest x ray. Another view of the mass visualized in Fig 1



Fig 3 Arterial phase of pulmonary angiography showing a hypoplastic right superior lobar artery



Fig 4 Venous phase of right pulmonary angiography. The superior lobar vein is absent and the dilated inferior lobar vein is opacified corresponding to the detected mass in the simple chest x ray

## Discussion

Pulmonary varix is an extremely rare entity of unknown origin. When it is found in symptomless individuals it is considered to stem from alterations in the development of the primitive splanchnic plexus.<sup>11</sup> In symptomatic patients with sustained pulmonary venous hypertension the varicosities were attributed to the venous hypertension.<sup>12,13</sup>

Its rate of presentation is unknown since generally it produces no symptoms. Most of the cases were diagnosed between the fourth and sixth decades, the ages ranging from 7 to 65 years.<sup>12</sup>

Pulmonary varix usually presents as a single mass though occasionally they are multiple having been reported in both lungs and anywhere within the lungs. The right upper pulmonary lobe is the commonest site of location.<sup>11,13,20,21</sup> The masses are symptomless otherwise a cardiopul

## Clinical pathologic conference

David H Spodick, M D  
Irwin K Kline M D  
Arthur J Press M D  
A N Moghadam M D  
Riaz A Akhtar M D  
Leonard M Drefus M D

Philadelphia Pa and Worcester Mass

**DR RIAZ A AKHTAR** A 28 year old white female electrocardiographic technician was admitted to Lankenau Hospital on December 26 1974 for refractory congestive heart failure

She was born in Poland but resided as a child in Argentina from 1957 to 1961 Her father had been treated for refractory supraventricular arrhythmia associated with left anterior hemiblock

In the fall of 1970 a routine ECG showed LBBB (Fig 1) The patient was asymptomatic until early 1972 when she complained of shortness of breath on exertion ankle swelling and fatigue The patient was admitted to the cardiac care unit with a heart rate of 30/minute and a high grade AV block The management included diuretics digitalization and the insertion of a permanent ventricular pacemaker with a demand rate of 60 pulses per minute (PPM) The patient was asymptomatic during the next two years but she returned to have the original demand pacemaker replaced by an atomic mode pacemaker (Model Medtronic No 9000) rate 74 PPM because of battery depletion of the original unit One month after atomic pacemaker replacement she noticed ankle edema shortness of breath and severe fatigue and palpitations A few weeks prior to the onset of symptoms she had an upper respiratory infection

On June 18 1974 cardiac catheterization revealed severely impaired left ventricular func-

tion LVEDP of 13 to 25 mm Hg normal coronary arteries and moderate mitral insufficiency resulting from mitral valve prolapse The pressures were AO = 84/58 mm Hg LV = 84/13 to 25 mm Hg peak dp/dt LV = resting 820 mm Hg/second and after exercise 730 mm Hg/second The electrocardiogram showed atrial flutter with high degree AV block and a ventricular rate controlled by the pacemaker at a rate of 74 PPM A sequential multiple analyzer of 12 vital determinations and a complete blood count on June 17 1974 were normal The immunoglobulins were as follows IgG = 135 mg per cent (normal 600 to 1300) IgA = 115 mg per cent (normal 50 to 300) IgM = 175 mg per cent (normal 50 to 250) A normal lipoprotein pattern was present The rheumatoid factor and antinuclear antibodies were negative A 2+ albumin was noticed in the urine with a specific gravity of 1017

The patient was treated with digoxin and diuretics and bed rest in view of her severely impaired ventricular function Subsequently she required repeat admissions for refractory congestive heart failure The final admission was on December 26 1974 because of severe fatigue congestive heart failure and bilateral pleural effusions At that time her blood pressure was 110/80 the pulse was 74 respiration was 18 temperature was 97 F and there was moderate jugular venous distension and 2+ pitting ankle edema On auscultation the lungs were clear but effusions were percussed at both lung bases A Grade 2/6 systolic murmur was heard at the lower sternal border which increased with expira-

From the Divisions of Pathology and Medicine The Lankenau Hospital, Philadelphia Pa. and Saint Vincent Hospital, Worcester Mass.

Received for publication April 25 1977

Reprint requests: Leonard M Drefus, M D Department of Cardiovascular Diseases, The Lankenau Hospital, Philadelphia Pa. 19151

- nary varicosities associated with coarctation of the aorta  
Thorax 25 97 1970
- 22 Hagen H and Heinz K A varicose node in the lingular  
branch of the pulmonary vein Fortschr Geb Roent  
genstr Nuklearmed 93 151 1960
- 23 Bryk D and Levin EJ Pulmonary varicosity Radiol  
ogy 85 834 1965
- 24 Gottesman L and Weinstein A Varicosities of the  
pulmonary veins Case report and survey of the litera  
ture Dis Chest 35 322 1959
- 25 Vengsarkar A S Kincaid O W and Weidman W H  
Selective angiocardiology in diagnosis of varicosity of  
the pulmonary veins Report of a case Am Heart J  
66 396 1963
- 26 Steinberg I Pulmonary varices mistaken for pulmonary  
and hilar disease Am J Roentgenol Radium Ther Nucl  
Med 101 947 1967
- 27 Perret L and Fortelhus P Ruptured aneurysm of a  
pulmonary vein Acta Tuberc Scand 41 53 1961

## Clinical pathologic conference

David H Spodick M D  
Irwin K Kline M D  
Arthur J Press M D  
A N Moghadam M D  
Riaz A Akhtar M D  
Leonard S Dreifus M D

Philadelphia Pa and Worcester Mass

**DR RIAZ A AKHTAR** A 28 year old white female electrocardiographic technician was admitted to Lankenau Hospital on December 26 1974 for refractory congestive heart failure

She was born in Poland but resided as a child in Argentina from 1907 to 1961 Her father had been treated for refractory supraventricular arrhythmia associated with left anterior hemiblock

In the fall of 1970 a routine ECG showed LBBB (Fig 1) The patient was asymptomatic until early 1972 when she complained of shortness of breath on exertion ankle swelling and fatigue The patient was admitted to the cardiac care unit with a heart rate of 30/minute and a high grade AV block The management included diuretics digitalization and the insertion of a permanent ventricular pacemaker with a demand rate of 60 pulses per minute (PPM) The patient was asymptomatic during the next two years but she returned to have the original demand pacemaker replaced by an atomic mode pacemaker (Model Medtronic No 9000) rate 74 PPM because of battery depletion of the original unit One month after atomic pacemaker replacement she noticed ankle edema shortness of breath and severe fatigue and palpitations A few weeks prior to the onset of symptoms she had an upper respiratory infection

On June 18 1974 cardiac catheterization revealed severely impaired left ventricular func-

tion LVEDP of 13 to 25 mm Hg normal coronary arteries and moderate mitral insufficiency resulting from mitral valve prolapse The pressures were AO = 84/58 mm Hg LV = 84/13 to 25 mm Hg peak dp/dt LV = resting 820 mm Hg/second and after exercise 730 mm Hg/second The electrocardiogram showed atrial flutter with high degree AV block and a ventricular rate controlled by the pacemaker at a rate of 74 PPM A sequential multiple analyzer of 12 vital determinations and a complete blood count on June 17 1974 were normal The immunoglobulins were as follows IgG = 135 mg per cent (normal 600 to 1300) IgA = 115 mg per cent (normal 50 to 300) IgM = 175 mg per cent (normal 50 to 250) A normal lipoprotein pattern was present The rheumatoid factor and antinuclear antibodies were negative A 2+ albumin was noticed in the urine with a specific gravity of 1017

The patient was treated with digoxin and diuretics and bed rest in view of her severely impaired ventricular function Subsequently she required repeat admissions for refractory congestive heart failure The final admission was on December 26 1974 because of severe fatigue congestive heart failure and bilateral pleural effusions At that time her blood pressure was 110/80 the pulse was 74 respiration was 18 temperature was 97° F and there was moderate jugular venous distension and 2+ pitting ankle edema On auscultation the lungs were clear but effusions were percussed at both lung bases A Grade 2/6 systolic murmur was heard at the lower sternal border which increased with expira-

From the Divisions of Pathology and Medicine The Lankenau Hospital, Philadelphia Pa and Saint Vincent Hospital Worcester Mass Received for publication April 1977

Reprint requests: Leonard S Dreifus M D Department of Cardiac Disease, The Lankenau Hospital, Philadelphia Pa. 19151

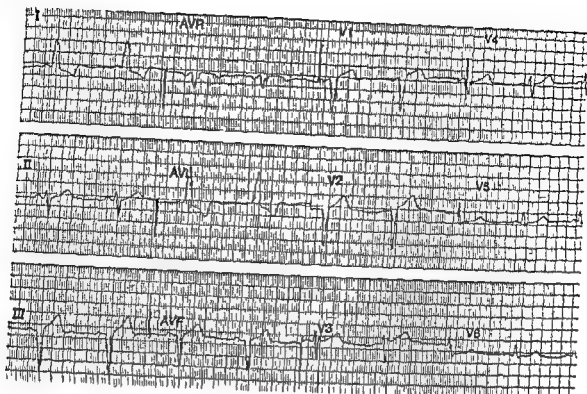


Fig 1 Electrocardiogram made in the fall of 1970 showing LBBB

tion Abdominal examination revealed the liver with a round firm edge of four fingerbreadths below the right costal margin. Laboratory studies included a cholesterol of 120 mg per cent, blood glucose of 160 mg per cent, bilirubin of 2.4 mg per cent, and hemoglobin 13.0 Gm. The electrocardiogram showed atrial flutter, high grade AV block, and an electronic pacemaker rate of 74 PPM. The chest x-ray showed a progressive increase in cardiomegaly since her past admissions, bilateral pleural effusions, and a possible pericardial effusion. An echocardiogram confirmed the pericardial effusion and suggested the amount was approximately 260 ml (Fig 2). Despite management with bed rest, diuretics, fluid restriction, her clinical progress was rather discouraging.

On January 9, 1975, an acute pulmonary embolism was suspected and was confirmed by lung scan. Heparin was started but had to be discontinued because the partial thromboplastin time rose from 34 to 106 seconds with a small dose of 5000 units. Ecchymosis and diffuse petechiae were noted over all regions of her body. A hematological survey for disseminated intravascular coagulation was negative. A gum biopsy was negative for amyloid. The patient developed a spiking temperature of 103° F. However, repeated cultures of blood, sputum, and urine failed to reveal any organism. Evaluation for a leak of radioactivity proved negative.

Clinical deterioration continued with fever, refractory congestive heart failure, cardiomegaly, and subsequent pulmonary emboli. The hemoglobin dropped progressively to 8.4 Gm on February 7, 1975, and the white blood count increased to 26,000. The bilirubin was 3.5 mg per cent, SGOT 250 units, LDH 600 units, and alkaline phosphatase was 175 units. The patient became comatose on February 6, 1975, and died on February 7, 1975.

DR DAVID H. SPODICK: I would be particularly interested to see an ordinary chest film and films of any other structures, for example the hands. I would also be interested in actually examining the cineangiograms and the other catheterization data.

DR ARTHUR PRESS: Serial chest radiographs show progressively increasing heart size, congestive changes, and finally pulmonary and pleural abnormalities leading to demise. Admission chest x-ray on June 11, 1974 (Fig 3) exhibits mild to moderate general cardiac enlargement, including left atrial fullness and minimal increased upper lung perfusion. A transvenous atomic model pacer is positioned in the right ventricle. Four months later the heart size is increased and there is slightly greater passive pulmonary congestion along with suggestive activities as judged by loss of the postero-inferior liver angle and separation of the lateral ascending

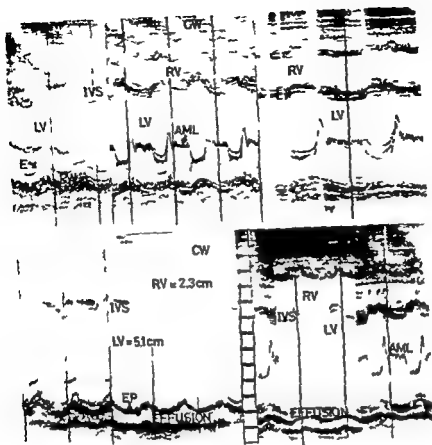


Fig 2 Echocardiogram CW = chest wall RV = right ventricle LV = left ventricle IVS = intraventricular septum AML = anterior leaflet of the mitral valve EP = posterior endocardium

colon contour from the adjacent preperitoneal fat. At the second admission on December 27, 1974, the heart is still more globular in shape. Pericardial fluid is a possibility but general chamber dilatation can account for the findings. Subpulmonic effusions have developed along with the mild passive pulmonary changes. On the fourteenth hospital day (January 10, 1975), dramatic pulmonary opacities are seen (Fig 4). The entire left lower lobe is consolidated and a small quantity of pleural fluid is identified on a decubital film. Two peripheral nodular lesions about 2.5 cm in size are seen in the right lung. While the left lung process is nonspecific, the right lung pleural base opacities suggest embolic phenomena.

**DR SPODICK:** Let us now examine the protocol for individual clues and diagnostic giveaways. She was born in Poland but lived for many years in Argentina. One thing that is common to both places is echinococcosis (Argentina has Chagas

Disease but this usually produces RBBB and this patient had LBBB). The electrocardiogram later shows left axis deviation as well as LBBB. Further analysis shows a QRS axis of  $-40$  degrees. The P waves are not unusual.

She was apparently well for a few years and then presents with congestive heart failure and complete AV block with a ventricular rate of 30 beats per minute. She might well have had one or more murmurs (owing to large stroke volume and progression of disease) but no murmurs are described at that time. No third heart sound was heard, which is unusual in the presence of advanced structural and functional cardiac abnormality. In the presence of LBBB, the first heart sound should have been of poor quality and the second heart sound might have split paradoxically but these were not described. The protocol does not mention lymphadenopathy, a sign of widespread diseases like lymphoma. Hence the disease process may well have been limited to the



Fig 3 Chest x ray made on June 17 1974 First admission chest x ray shows mild to moderate globular cardiac enlargement minimal blood flow cephalization and a right ventricular pacemaker



Fig 4 Chest x ray made on Jan 10 1975 second hospitalization 14th day Extensive left lower lobe consolidation minimal effusion and two poorly margined peripheral right lung nodules The heart is larger and more globular but its base has not widened appreciably

mediastinum and lungs X ray films of the hands did not reveal findings which could have pointed to sarcoid or the connective tissue disease group The presence of upper respiratory infection (URI) may or may not have been significant in the subsequent events frequently a URI is a red herring In 1974 she had a cardiac catheterization May I see the data?

DR AN MOGHADAM Cardiac catheterization consists of left ventriculography left heart catheterization and coronary cineangiography The end diastolic pressure of the left ventricle was 24 mm Hg The systemic pressure was 84 mm Hg in the aorta and left ventricle There was dysfunction of the left ventricle and prolapse of the mitral valve There was some mitral insufficiency seen on the ventriculogram which could be due either to papillary muscle dysfunction or to asynchronous activation of the atria and ventricle in the presence of the permanent pacemaker The tracing is a square root form with a sudden termination of filling and a plateau No pericardial effusion is seen at the time of catheterization

DR SPODICK Catheterization has settled a number of questions There is a decreased  $dp/dt$

a poorly functioning dilated left ventricle and mitral insufficiency, as expected despite the absence of a murmur

The sequential multiple analyzer of 12 vital determinations at that time was normal including notably a normal serum albumen Both rheumatoid factor and antinuclear antibody titers are negative The 2+ albumin in the urine may be explained by congestive heart failure Studies shows decreased IgG That reduction can be due to decreased synthesis, increased catabolism or both The lipoprotein pattern is normal

What do the bedside findings tell us? The patient developed increasing congestive heart failure and begins a rapid downhill course characterized by mainly right sided circulatory congestion without definite findings indicating left heart failure (You must have right heart 'success' to exhibit left heart failure) Pericardial effusion with cardiac tamponade for example could be a cause of systemic venous congestion and indeed there was considerable venous distention and the echocardiogram indicated some pericardial fluid Now for the first time in this seriously ill young woman a systolic murmur is mentioned Specifically a Grade 2/6 murmur at

the left lower sternal border which increased with expiration. If this observation was accurate and if that was not a pericardial rub (which in about 30 per cent of patients can be louder on expiration) we can imagine rather odd causes such as tricuspid valve prolapse since the right ventricle would underfill during expiration. The liver and neck veins did not pulsate which would have been expected for tricuspid regurgitation. Ordinary tricuspid valvular incompetence by contrast produces louder murmurs in inspiration. Another possibility is right ventricular obstructive cardiomyopathy with this type of expiratory exacerbation of the murmur although that would be an equally odd cause. The murmur could have been due to an angulated jet effect from a mitral prolapse but that should not increase during expiration. Finally, the appearance *de novo* of such a murmur at the left lower sternal border in conjunction with the catastrophic preterminal cardiocirculatory events could also be consistent with perforation by the disease process of the interventricular septum with a left to right shunt however no thrill was described.

What does the echocardiogram tell us? The echocardiographic dimensions are upper normal for both ventricles. Hence this cannot be a very dilated heart. There is posterior pericardial effusion in this echocardiogram. Since the effusion does not appear anteriorly I would conclude that it is rather small and less likely to be causing cardiac compression. The mitral valve echogram indicated prolapse with the anterior leaflet thrown posteriorly during systole (there is no tricuspid valve tracing). Ventricular wall movement looks poor with paradoxical septal motion. This could be due to right ventricular volume overload but her pacemaker could have produced this since there is stimulation first of the right ventricle—the physiologic equivalent of delayed stimulation of the left ventricle. In summary, the echocardiogram only adds one fact to our knowledge, i.e. that the cardiomegaly is partly due to pericardial effusion. Left atrial size was normal in the echocardiogram yet there was a density on the chest film in keeping with left atrial enlargement.

What do the lung scans tell us? Multiple pulmonary emboli are confirmed by lung scan. In view of the peculiar constellation of clinical and laboratory findings the source of these pulmonary emboli becomes more interesting, i.e. it

could be the right heart or the systemic veins. The patient had a very poor response to heparin with her partial thromboplastin time rising sharply. This could also be explained on the basis of abnormal liver function. She did not have disseminated intravascular coagulation.

She developed spiking temperatures and this I assume was in the presence of multiple negative blood cultures. The tuberculin test was negative. The negative radiation physics studies rules out a leaky atomic pacemaker. We are fairly certain that she did not have a protein losing enteropathy. There was no evidence of bleeding to account for the dropping hemoglobin. Terminally she spiked a very high white blood cell count (could the fever have been due to leukocytic pyrogen?).

Can we discern relationships among her long standing and more recent signs and symptoms? This is indeed a complex series of events each of which requires some explanation and an attempt to make sense of any patterns. We must explain pre-existing LBBB progressing to high grade A V block. I am not aware of isolated congenital LBBB. Though it may exist I think we consider virtually every case at any age to be acquired. Here there is a very abnormal left ventricle as well as LBBB making this certainly an instance of intrinsic left ventricular disease. Mitral prolapse by echocardiogram was present without a murmur or a click; the ventricle was not severely enlarged. Mitral regurgitation with ordinary congestive cardiomyopathy is nearly always associated with a disproportionately large left ventricular volume and left papillary muscle involvement can occur in infiltrative cardiomyopathy which is more likely to have a smaller ventricular volume. Was the mitral prolapse a part of an unrelated click-murmur syndrome in which there is ventriculovalvular disproportion or is the prolapse due to acquired disease (cardiomyopathy involving or distorting the mitral supporting structures)? The possibility of artifactual echocardiographic prolapse must also be considered especially in the presence of pericardial effusion. However this usually occurs with cardiac tamponade. Finally, tamponading pericardial effusion would have affected the heart sounds and might have caused the loss of any S<sub>2</sub> which was indeed absent despite several cardiac abnormalities. The echo shows no evidence of a swinging heart and there was no pulsus para-





Fig 3 Chest x ray made on June 17 1974 First admission chest x ray shows mild to moderate globular cardiac enlargement minimal blood flow cephalization and a right ventricular pacemaker



Fig 4 Chest x ray made on Jan 10 1975 second hospitalization 14th day Extensive left lower lobe consolidation minimal effusion and two poorly margined peripheral right lung nodules The heart is larger and more globular but its base has not widened appreciably

mediastinum and lungs X ray films of the hands did not reveal findings which could have pointed to sarcoid or the connective tissues disease group The presence of upper respiratory infection (URI) may or may not have been significant in the subsequent events, frequently a URI is a red herring In 1974 she had a cardiac catheterization May I see the data?

DR A N MOGHADAM Cardiac catheterization consists of left ventriculography left heart catheterization, and coronary cineangiography The end diastolic pressure of the left ventricle was 24 mm Hg The systemic pressure was 84 mm Hg in the aorta and left ventricle There was dysfunction of the left ventricle and prolapse of the mitral valve There was some mitral insufficiency seen on the ventriculogram which could be due either to papillary muscle dysfunction or to asynchronous activation of the atria and ventricle in the presence of the permanent pacemaker The tracing is a square root form with a sudden termination of filling and a plateau No pericardial effusion is seen at the time of catheterization

DR SPODICK Catheterization has settled a number of questions There is a decreased  $dP/dt$

a poorly functioning dilated left ventricle and mitral insufficiency, as expected despite the absence of a murmur

The sequential multiple analyzer of 12 vital determinations at that time was normal, including notably a normal serum albumen Both rheumatoid factor and antinuclear antibody titers are negative The 2+ albumin in the urine may be explained by congestive heart failure Study shows decreased IgG That reduction can be due to decreased synthesis increased catabolism or both The lipoprotein pattern is normal

What do the bedside findings tell us? The patient developed increasing congestive heart failure and begins a rapid downhill course characterized by mainly right sided circulatory congestion without definite findings indicating left heart failure (You must have right heart success to exhibit left heart failure) Pericardial effusion with cardiac tamponade for example could be a cause of systemic venous congestion and indeed there was considerable venous distention and the echocardiogram indicated some pericardial fluid Now for the first time in this seriously ill young woman a systolic murmur is mentioned Specifically a Grade 2/6 murmur at

the left lower sternal border which increased with expiration. If this observation was accurate and if that was not a pericardial rub (which in about 30 per cent of patients can be louder on expiration) we can imagine rather odd causes such as tricuspid valve prolapse since the right ventricle would underfill during expiration. The liver and neck veins did not pulsate which would have been expected for tricuspid regurgitation. Ordinary tricuspid valvular incompetence by contrast produces louder murmurs in inspiration. Another possibility is right ventricular obstructive cardiomyopathy with this type of expiratory exacerbation of the murmur although that would be an equally odd cause. The murmur could have been due to an angulated jet effect from a mitral prolapse but that should not increase during expiration. Finally the appearance *de novo* of such a murmur at the left lower sternal border in conjunction with the catastrophic preterminal cardiovascular events could also be consistent with perforation by the disease process of the interventricular septum with a left to right shunt however no thrill was described.

What does the echocardiogram tell us? The echocardiographic dimensions are upper normal for both ventricles. Hence this cannot be a very dilated heart. There is posterior pericardial effusion in this echocardiogram. Since the effusion does not appear anteriorly I would conclude that it is rather small and less likely to be causing cardiac compression. The mitral valve echogram indicated prolapse with the anterior leaflet thrown posteriorly during systole (there is no tricuspid valve tracing). Ventricular wall movement looks poor with paradoxical motion. This could be due to right ventricular volume overload but her pacemaker could have produced this since there is stimulation first of the right ventricle—the physiologic equivalent of delayed stimulation of the left ventricle. In summary the echocardiogram only adds one fact to our knowledge i.e. that the cardiomegaly is partly due to pericardial effusion. Left atrial size was normal in the echocardiogram yet there was a density on the chest film in keeping with left atrial enlargement.

What do the lung scans tell us? Multiple pulmonary emboli are confirmed by lung scan. In view of the peculiar constellation of clinical and laboratory findings the source of these pulmonary emboli becomes more interesting i.e. it

could be the right heart or the systemic veins. The patient had a very poor response to heparin with her partial thromboplastin time rising sharply. This could also be explained on the basis of abnormal liver function. She did not have disseminated intravascular coagulation.

She developed spiking temperatures and this I assume was in the presence of multiple negative blood cultures. The tuberculin test was negative. The negative radiation physics studies rules out a leaky atomic pacemaker. We are fairly certain that she did not have a protein losing enteropathy. There was no evidence of bleeding to account for the dropping hemoglobin. Terminally she spiked a very high white blood cell count (could the fever have been due to leukocytic pyrogen?)

Can we discern relationships among her long standing and more recent signs and symptoms? This is indeed a complex series of events each of which requires some explanation and an attempt to make sense of any patterns. We must explain pre-existing LBBB progressing to high grade A V block. I am not aware of isolated congenital LBBB. Though it may exist I think we consider virtually every case at any age to be acquired. Here there is a very abnormal left ventricle as well as LBBB making this certainly an instance of intrinsic left ventricular disease. Mitral prolapse by echocardiogram was present without a murmur or a click the ventricle was not severely enlarged. Mitral regurgitation with ordinary congestive cardiomyopathy is nearly always associated with a disproportionately large left ventricular volume and left papillary muscle involvement can occur in infiltrative cardiomyopathy which is more likely to have a smaller ventricular volume. Was the mitral prolapse a part of an unrelated click-murmur syndrome in which there is ventriculovalvular disproportion or is the prolapse due to acquired disease (cardiomyopathy involving or distorting the mitral supporting structures)? The possibility of artifactual echocardiographic prolapse must also be considered especially in the presence of pericardial effusion. However this usually occurs with cardiac tamponade. Finally tamponading pericardial effusion would have affected the heart sounds and might have caused the loss of any S<sub>2</sub> which was indeed absent despite several cardiac abnormalities. The echo shows no evidence of a swinging heart and there was no pulsus para-

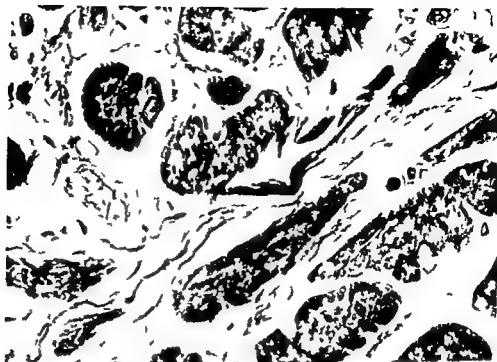


Fig 5 Interstitial fibrosis surrounding individual muscle fibers and interrupting their longitudinal course (Masson stain original magnification  $\times 540$ )

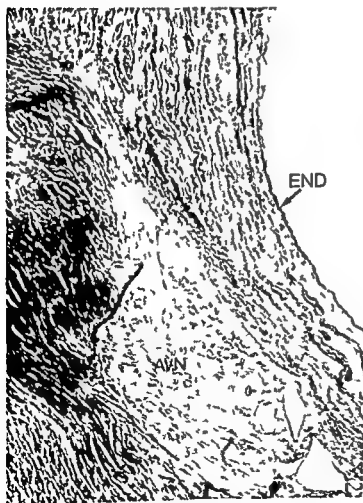


Fig 6 Terminal portion of A V node (left of center towards left lower corner) surrounded by dense fibrosis AVN = AV node END = endocardium (Masson elastic stain original magnification  $\times 37$ )

doxus, more data against cardiac tamponade. The main difficulty arising from the presence of pericardial effusion is the decision as to its origin, i.e., was it inflammatory or associated with congestive heart failure?

The terminal events including the spiking fever suggest blood stream invasion by pyrogenic material, however, all cultures were negative. Despite this could this represent an infective endocarditis? It is particularly noteworthy that this occurred in the setting of preterminal pulmonary emboli. Could a single catastrophe account for both blood stream invasion and pulmonary emboli? I shall return to this later.

How to explain the progressive conduction system abnormality culminating in high grade A V block? Auto immune disease of the conduction system (Idiopathic Fibrosis) is frequent but usually occurs in much older patients. This patient may have had an immunopathy touched off by a viral or other infection. However the IgG would have risen and other proteins decreased so that this does not seem likely. She lived in two countries in which echinococcosis is common and afflicts the heart, the pericardium and the liver. In the absence of eosinophilia I think this is highly unlikely. Could a connective tissue disorder account for the myocardial valvular, and conduction system lesions? This is entirely possible in a young woman. Scleroderma heart

disease could equally be involved accounting for cardiac restriction the conduction abnormalities and the pericardial effusion. Yet patients with scleroderma nearly always have prominent skin involvement and gastrointestinal problems and she did not. Adult fibroelastosis and endomyocardial fibrosis seem unlikely in the absence of a prominent third heart sound.

These significant rule outs leave us essentially with a disease of the walls of the heart i.e. a cardiomyopathy of some kind since there is no evidence of large or small vessel disease or of predominantly valvular or pericardial disease. What valve malfunction there was could not explain the picture. So this is a cardiomyopathy but probably not a primary disease of the heart muscle itself. What kind of cardiomyopathy? Restrictive. What kind of process causing restriction? This probably represents an infiltrative process a lesion that spreads in the myocardium and that tends to end in biventricular failure involving in the process the septum and conduction system and ultimately the mitral supporting structures. What kind of infiltration? Possibilities include lymphoma, sarcoid or a subacute infectious process. Amyloid is another infiltration but this is a fairly young patient and patients with amyloid disease tend to be considerably older or have other chronic diseases. You can have amyloid of the pericardium or the valves in unusual cases but her gum biopsy was negative and I would rule out amyloidosis. There was no evidence for connective tissue disease or lymphoma. Therefore this may be an inflammatory process i.e. a myocarditis. What kind of inflammation? Given the tempo of progression of this syndrome a relatively slow granulomatous type of infiltrative process seems likely. There are a number of these including the so called idiopathic giant cell myocarditis seen in young people with conduction abnormalities. Tuberculous myocarditis must also be considered. It is not common. There are three forms—the large caseous type the miliary type (but this usually occurs in the presence of miliary spread) or a diffuse infiltration. Diffuse tuberculous myocarditis advances slowly but ultimately involves the heart widely and also involves the conduction system. You could construct a scenario that could account for the terminal events including the eventual loud murmur and the pulmonary infarctions. One could hypothesize (or fantasize!) that the

myocardial lesions ruptured the septum. Now you could postulate that thrombotic material forming on the right side of the injured septum produced the pulmonary emboli. With the hypothetical septal rupture infectious material could spread into the blood stream and a terminal miliary process could be seen in the liver and elsewhere. This is one of the two possibilities. The other possibility is sarcoid. I would rather like sarcoid particularly in the absence of the murmur with a similar picture of AV block liver involvement and atrial arrhythmias as well as congestive failure. The terminal events could be due to hemorrhage and central nervous system involvement. But in sarcoid the IgG is elevated not down as in this case.

With all the foregoing in mind it is time for conclusions. We are dealing with a restrictive myocardiopathy which is secondary specifically infiltrative. What kind of infiltration? Inflammatory. What kind of inflammation? Granulomatous and probably with giant cells. Therefore a chronic or subacute myocarditis. My first choice is diffuse tuberculous myocarditis. Second choice sarcoid. Complications pulmonary emboli probably from the right heart.

DR IRWIN K. KLINE. The patient was a very slender and small woman about 4 ft 8 in in height. The autopsy revealed a hypertrophied as well as dilated heart weighing 360 Gm containing mural thrombi both in the right and left ventricles. The coronary arteries were patent throughout and a pacemaker electrode was impaled in the cavity of the right ventricular apex. The endocardium of the left ventricle was moderately thickened and the left ventricular free wall was of increased thickness. There was definite stiffness to the entire heart.

The outstanding feature on microscopic examination was the presence of moderate to marked hypertrophic myofibers many of which were surrounded by slender strands of fibrous tissue and occasionally interrupting the course of individual muscle fibers (Fig 5). This is the picture most commonly seen with a post viral myocarditis. In addition no parasites of the Chagas variety were noted. Nor were there any stellate scars which would be indicative of the post Chagas type of cardiomyopathy. These scars are readily apparent as noted in both experimental and clinical studies from South America.

The conduction system was examined to corre-

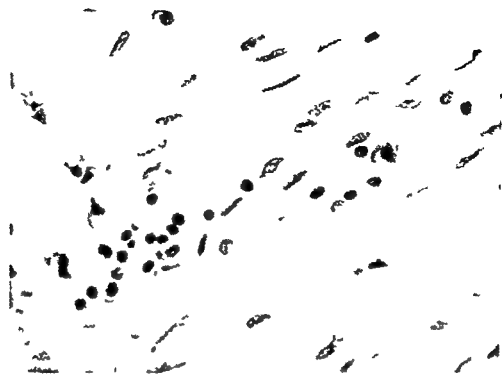


Fig 7 Interstitial myocarditis composed of lymphocytes with an occasional mast cell and some Anitschkow myocytes in edematous tissues (Hematoxylin and eosin original magnification  $\times 540$ )

late the anatomic findings with the clinical irregularities. Serial sections revealed that the A V node as well as the bundle of His were both surrounded and focally interrupted by chronic fibrosis (Fig 6). In addition, several areas of active myocarditis were noted where the interstitial tissue contained numerous round cells, primarily lymphocytes with occasional Anitschkow myocytes and mast cells (Fig 7). Several organizing microinfarctions were present in the high septum and fairly close to the conduction system. These microinfarctions are most likely due to coronary emboli resulting from the left ventricular mural thrombus.

Terminally there were multiple pulmonary emboli with pulmonary infarctions as well as renal infarctions. These emboli had their origin in the right and left ventricles respectively. The liver showed a typical congestive nutmeg pattern due to marked right ventricular failure. The other organs showed no gross or microscopic abnormalities and examination of the brain was not permitted.

In summary this was a case of a restrictive cardiomyopathy or a chronic active myocarditis of the so called pernicious variety which is most

likely post viral in etiology. Although viruses could not be cultured from this case, the microscopic appearance of the individual muscle fiber replacement and slender strands of fibrous tissue surrounding individual muscle fibers is highly suggestive of this type of process. The foci of active myocarditis indicates the self-perpetuating type of lesion that may be present in such cases. These foci lead to exacerbations which is part of the clinical picture. Unfortunately each exacerbation is worse than the preceding and the patient's demonstrate a relentless downhill course. Mural thrombi often contribute to the sudden ending as exemplified in this case.

**Final diagnosis** Restrictive cardiomyopathy or chronic active myocarditis of the so called pernicious variety possibly post viral in etiology, congestive heart failure, AV block, multiple pulmonary emboli with pulmonary and renal infarctions.

#### REFERENCES

- 1 Kline J H and Saphir O. Chronic pernicious myocarditis. *Am HEART J* 59:681 1960.
- 2 Gore I and Kline J H. Chapter on myocarditis. In: *Pathology of the heart and blood vessels* third edition S F Gould editor Springfield Ill 1968 Charles C Thomas Publisher pp 731-759.

New Orleans La

In spite of the above difficulties in understanding congestive heart failure no well trained clinician has difficulty in recognizing the signs and symptoms of congestive heart failure at the

Sponsored by Grant HL-14-89 from the National Institutes of Health  
of the United States Public Health Service through the National Institute of Mental Health.  
Major funding provided by the Center for Research in Human Development, University of California,  
Berkeley.

Reprint request: C. F. III, c/o BFD, T. Lane L., Jr., School of  
Medicine, 1430 T. La. Ave., New Orleans, La. 70112

0002 8-03/78/0295-025. 400 70/0 8-10-78 The C & Mosby Co



Fig 7 Interstitial myocarditis composed of lymphocytes with an occasional mast cell and some Anitschkow myocytes in edematous tissues (Hematoxylin and eosin original magnification  $\times 540$ )

late the anatomic findings with the clinical irregularities. Serial sections revealed that the AV node as well as the bundle of His were both surrounded and focally interrupted by chronic fibrosis (Fig 6). In addition, several areas of active myocarditis were noted where the interstitial tissue contained numerous round cells primarily lymphocytes with occasional Anitschkow myocytes and mast cells (Fig 7). Several organizing microinfarctions were present in the high septum and fairly close to the conduction system. These microinfarctions are most likely due to coronary emboli resulting from the left ventricular mural thrombus.

Terminally there were multiple pulmonary emboli with pulmonary infarctions as well as renal infarctions. These emboli had their origin in the right and left ventricles respectively. The liver showed a typical congestive nutmeg pattern due to marked right ventricular failure. The other organs showed no gross or microscopic abnormalities and examination of the brain was not permitted.

In summary, this was a case of a restrictive cardiomyopathy or a chronic active myocarditis of the so called pernicious variety which is most

likely post viral in etiology. Although viruses could not be cultured from this case the microscopic appearance of the individual muscle fiber replacement and slender strands of fibrous tissue surrounding individual muscle fibers is highly suggestive of this type of process. The foci of active myocarditis indicates the self-perpetuating type of lesion that may be present in such cases. These foci lead to exacerbations which is part of the clinical picture. Unfortunately each exacerbation is worse than the preceding and the patients demonstrate a relentless downhill course. Mural thrombi often contribute to the sudden ending exemplified in this case.

**Final diagnosis:** Restrictive cardiomyopathy or chronic active myocarditis of the so called pernicious variety possibly post viral in etiology, congestive heart failure, AV block, multiple pulmonary emboli with pulmonary and renal infarctions.

#### REFERENCES

1. Kline I K and Saphir O. Chronic pernicious myocarditis. *AM HEART J* 59:681 1960.
2. Gore I and Kline I K. Chapter on myocarditis in *Pathology of the heart and blood vessels*, third edition S. M. Gould editor, Springfield, Ill 1963, Charles C Thomas Publisher, pp 731-739.

constriction in CHF is evident to any astute clinician by the moist pale skin

Perhaps before and certainly when venous tone is increased renal sodium and water retention develops. The retention of sodium and water seems to be the result of a dual mechanism. First because of the inadequate cardiac output blood is shunted away from the kidneys so that the kidneys receive a smaller proportion of the cardiac output than during normal heart function—reflection of a compensatory action of the CNS and autonomic nervous system. The decreased renal blood flow is therefore due to constriction of the afferent and efferent arterioles of the glomeruli. Glomerular filtration rate (GRF) is reduced in absolute terms but is increased relative to renal blood flow (RBF). The filtration fraction (GRF/RBF) is increased because efferent arteriolar constriction is greater than afferent arteriolar constriction. Thus just as the decrease in renal blood flow reflects sympathetic nervous system activity so the increase in the filtration fraction is a reflection of sympathetic nervous system activity which results in a disproportionate constriction of the afferent and efferent arterioles. Under such circumstances proximal tubular reabsorption of sodium is increased and the quantity of sodium excreted in the urine is decreased.

The second mechanism responsible for the retention of sodium and water is related to the influence of adrenal hormones on the renal tubules. Although the role of the adrenal hormones in the sodium and water retention of congestive heart failure is not completely understood it is possible to devise a working hypothesis as follows:

Due to decreased pulsatile distension of the juxtaglomerular apparatus renin is released from the juxtaglomerular apparatus. Renin in turn activates angiotensin from the alpha 2 globulin of the plasma and angiotensin stimulates the adrenal gland to secrete aldosterone. The efferent stimulus for the secretion of aldosterone by the adrenal gland is decreased pulsatile distension of the juxtaglomerular apparatus is mediated through the CNS and autonomic nervous system.

#### Influence of the nervous system on venous tone

As already stated it is believed but not established that as cardiac output becomes inadequate

relative to the needs of the body, venous tone increases and systemic venous return and ventricular filling pressure increase resulting in an augmentation of cardiac output. It is necessary at this point to define the term venous tone as well as to review the mechanisms by which venous tone is regulated by the nervous system.

**Venous tone** To use simple terms we shall consider basal or static venous smooth muscle tone functionally to be an expression of the basal or static tightness with which the wall of a vein fits around the column of blood within. However the dimension size or caliber of the column of blood in a vein does not necessarily reflect the tone of the smooth muscle of the wall of the vein. For that matter the tone of a venous segment which is engorged with blood may be high or low. Furthermore in an open segment of vein the venous pressure may not necessarily reflect the level of the venous tone of that segment.

In more mechanical terms venous tone may be defined as the ability of a vein to resist deformation (strain) when subjected to a distorting force (stress). Deformation is usually considered as the percentage change in length of a material produced by a given stress (usually a weight suspended from the material). However for a blood vessel the percentage change in length is more conveniently considered as the percentage change in radius whereas the distorting force is expressed as a change in tension within the wall of the vessel. The tension or tangential stress (T) within the venous wall is defined as

$$T = P(r/h) \quad (1)$$

where  $P$  is the difference between the intravascular and extravascular pressures i.e. the distending pressure,  $r$  is the radius of the lumen of the vessel and  $h$  is the thickness of the wall of the vessel. Thus venous tone is mechanically determined by those factors contributing to the tightness or stiffness of the venous wall which determines the radius of the vein at a given tension. The most important factors contributing to the stiffness or tightness of the vein may be expressed by the moduli of elasticity and viscosity of the venous wall and by the geometry of the wall ( $r/h$ ).

It should be clear that tone and distensibility are different functions. Distensibility (D) is defined by the relationship

$$D = (\Delta P / \Delta V) V \quad (2)$$

where  $\Delta P$  is the change in applied pressure,  $\Delta V$  is



It is probable that the fundamental subcellular disturbances which occur within the myocardium in congestive heart failure precede any measurable circulatory or hemodynamic alterations. The methods for measuring such alterations are crude. Thus the various hemodynamic disturbances which occur in congestive heart failure must be considered as late manifestations of congestive heart failure. To a great extent the circulatory alterations in congestive heart failure appear to be compensatory. However, in the later stages of failure these compensatory alterations overburden the heart so that a vicious cycle is instituted which if left uninterrupted, ends in the death of the entire organism.

Many of the most important compensatory responses to congestive heart failure are mediated through the nervous system (the greatest integrator of organ functions in the body) particularly the autonomic nervous system. The purpose of this report is to summarize some of the present knowledge regarding the role of the nervous system in congestive heart failure.

#### Fundamental clinical alterations associated with chronic Congestive Heart Failure

Before describing the role of the nervous system in congestive heart failure it is advisable to review some of the fundamental alterations which occur in congestive heart failure.

The heart responds to an increased load in at least one or more of four ways namely (1) hypertrophy, (2) increase in stroke volume (3) increase in heart rate, and (4) increase in rate of effort force or work (power) of myocardial contraction. It should be noted that the nature of the load may vary among patients with CHF i.e. there may be a pressure overload (as with hypertension valvular stenosis) or a volume overload (as with anemia hyperthyroidism). Furthermore the load may be only relatively increased, i.e. the demands upon the myocardium are normal but because of destruction of some myocardial tissue these normal demands must be met by a smaller number of contractile units which must work with greater effort.

Depending upon the magnitude of the load its chronicity, and the state of the myocardium the compensatory adjustments may be adequate to meet the requirements of the tissues so that no clinical difficulties arise. On the other hand a point may be reached at which cardiac output is no longer adequate to meet the needs of all the

tissues. The cardiac output at first is inadequate only upon exercise or stress but it may eventually also become inadequate even at rest. At some time during the above chain of events the signs and symptoms of congestive heart failure develop. The failure of the cardiac pump may, at a time, involve only one ventricle, i.e. the stroke output of one ventricle may exceed that of the other ventricle. However, the output of one ventricle cannot exceed that of the other ventricle over a prolonged period of time.<sup>2</sup> Whether the healthy ventricle actually fails in a given patient or merely readjusts its volume output to that of the diseased ventricle is a question which has not received adequate consideration but is beyond the scope of this discussion and involves measurements which are impossible to obtain accurately with existing methods. It should be understood that in failure of the cardiac pump the cardiac output is considered to be inadequate to meet the needs of all the tissues important among which are probably certain crucial regulatory tissues such as the central nervous system (CNS). The cardiac output may be normal at rest, or in so called "high output failure," it may even be increased at rest. Nevertheless an increase in cardiac output adequate to meet the requirements of all the tissues does not occur upon exercise or stress.<sup>3, 4</sup>

When the cardiac output becomes inadequate to meet the requirements of all the tissues a new system of priorities must be established i.e. the circulation must be readjusted. The proportions of the cardiac output going to the kidneys and skin are readjusted so that these organs receive relatively less blood than in the non failing state whereas the controlling mechanisms apparently give necessary preference to the CNS. As will be indicated later in this discussion these readjustments are mediated largely through the central and autonomic nervous systems.

When the heart fails there is peripheral vasoconstriction and a compensatory increase in venous tone which are associated with an increase in systemic venous return as well as an increase in right ventricular filling pressure. For a while the increased filling pressure results in an augmentation of cardiac output. This response is not necessarily evoked by an increase in the load or demand placed upon the heart but may develop as a result of an imbalance between demand and the cardiac output of a diseased heart working with greater effort. The cutaneous vaso-

and carotid sinuses. Impulses arising in the aortic arch and carotid sinus receptors stimulate the inhibitory portion of the VMC which in turn inhibits the excitatory portion of the VMC so that sympathetic outflow is decreased.

The interaction of the various reflex pathways concerned with cardiovascular regulation may be illustrated by the following example. Let it be supposed that there is a sudden reduction in arterial blood pressure secondary to blood loss. As arterial blood pressure in the aorta and carotid sinuses declines stimulation of the pressor receptors in these vessels decreases and in turn the number of impulses reaching the inhibitory portion of the VMC from the pressor receptors also decreases. The inhibition of the excitatory portion of the VMC by the inhibitory center is diminished and sympathetic vasoconstrictor outflow increases. The increase in sympathetic outflow results in increased arteriolar tone so that the peripheral vascular resistance increases. In addition the capacitance vessels are constricted so that systemic venous return is increased (the volume of the peripheral venous reservoir is decreased). Finally the cardiac rate and the force and rate of myocardial contraction also are increased. The net result of these responses is an increase in cardiac output or rate of work (power output) and arterial blood pressure to pre hemorrhagic levels. In fact there may even be some degree of overshooting so that for a brief time arterial blood pressure is higher than before hemorrhage had occurred. The blood pressure is adjusted downwards by reversing the process described above.

There is some preliminary evidence that the influence of the sympathetic constrictor outflow may not be uniform throughout the cardiovascular system. For example the frequency response curve to gradually increased vasoconstrictor stimulation is different for the resistance than for the capacitance vessels. Thus for a given uniform sympathetic discharge constriction of the capacitance vessels may precede that of the resistance vessels. Furthermore with the exception of the venules the veins are less influenced by local factors than are the precapillary vessels i.e. the resistance vessels where local myogenic and local humoral activity may predominate or at least greatly modify sympathetic constrictor stimulation whereas in the larger veins at least

sympathetic vasoconstrictor control is dominant. As will be indicated later the concept that sympathetic vasoconstrictor activity may be so integrated that some segments of the circulation are influenced relatively more than others may help to provide answers to some disturbing questions regarding the role of the nervous system in congestive heart failure.

It should also be pointed out that the vaso motor center is influenced by impulses arising in the hypothalamus, cerebral cortex and elsewhere in the central nervous system. These central nervous impulses are responses to changes in function (physiochemical states) of the heart and circulation. It is well known that emotional disturbances may produce reflex changes in vascular tone. Although reflexes arising in the cerebral cortex may not independently play a role in the compensatory adjustments to congestive heart failure they certainly can modify these adjustments. The importance of conditioned and orienting cardiovascular reflexes in congestive heart failure is unknown. Again it is unlikely that conditioned and orienting reflexes play a major role in the pathogenesis of congestive heart failure in most patients. However such reflexes may modify the compensatory adjustments to the failing heart in all patients and may even precipitate congestive heart failure in some patients. The role of these and other reflexes in CHF certainly needs study.

The role of the central nervous system in Congestive Heart Failure. It is axiomatic that in chronic congestive heart failure the myocardium is diseased and dilated. It is true that constrictive pericarditis may result in a clinical pattern which resembles congestive heart failure in the absence of significant myocardial disease. Other exceptions also exist. Nevertheless to focus on the rare occasions in which congestive heart failure exists in the absence of a cardiac lesion and a dilated heart would only detract from the fact that in the overwhelming majority of patients with chronic congestive heart failure the heart muscle is diseased and the heart is dilated acutely or chronically. The heart disease in patients with congestive heart failure may be primarily disease of the heart itself or secondary to systemic disease.

Associated with failure of the compensatory phenomena described above i.e. hypertrophy, cardiac acceleration and increased force of

the volume change and  $V_0$  is the initial volume of the vessel. As already indicated the tone or stiffness of a vein is a function of the ratio of the radius of the vein to the wall thickness, i.e.,  $\text{Elastic stiffness} = \text{Tangential Stress} = P(r/h)$  (3). Because the large veins have a large radius as compared to wall thickness, they have relatively high moduli of elasticity. Thus a large vein may be highly distensible but may actually be 'stiffer' than an artery of comparable size.

It would appear that the basal tone or stiffness of the veins is set at a certain level by some 'catch mechanism' or 'ratchet mechanism' located in the contractile fibrillae of the smooth muscle in the venous wall whereby venous tone at any given level is 'set' or maintained for prolonged periods of time with low energy cost. Any intervention mediated through the CNS and autonomic nervous system which lowers or raises venous pressure is associated with a change in venous smooth muscle tone which tends to restore the venous pressure to the level that existed at any other given time.

Folkow<sup>1</sup> presented the interesting concept that because the precapillary resistance vessels subserve the local needs of the tissues these vessels possess a high degree of myogenic autoregulation. On the other hand, the larger veins (capacitance vessels), because they subserve the needs of the entire organism through their influence on venous return and cardiac output are predominantly under central and autonomic nervous system control. The intact veins of the human forearm display stress-relaxation and stress-relaxation recovery behavior.<sup>11</sup> These phenomena persist after anesthetic denervation of the vein. Thus decreasing the volume and pressure in an isolated venous segment will result in an increase in the tone of the venous wall which will, within limits, tend to restore the pressure in the segment to the initial levels. Thus the veins are capable of some degree of autoregulation in that they attempt to maintain pressure at a certain level in the presence of disturbing physiologic influences. However it should be understood that an increase or decrease in venous tone may occur with no change in the capacity of the venous reservoir. Mobilization of blood from or into the venous reservoir can only occur when the veins constrict or dilate. In this regard the veins as well as the peripheral blood vessels are

strongly influenced by the CNS and autonomic nervous system.

### Role of the nervous system in myocardial contractility

**Reflexes concerned with cardiovascular regulation.** The 'vasomotor center' (VMC) is not a discrete anatomic entity but is rather a diffuse area of cells located in the dorsolateral reticular formation of the medulla oblongata and other parts of the CNS. The vasomotor center may be divided into two functional parts namely an excitatory center and an inhibitory center. Impulses from the excitatory center are distributed both to the heart and blood vessels via the sympathetic nervous system whereas impulses from the inhibitory center are distributed to the heart via the parasympathetic nerves but to the blood vessels via the sympathetic nervous system (e.g., sympathetic vasodilator fibers). The excitatory and inhibitory portions of the vasomotor center are also mutually inhibitory.

Vasomotor tone is regulated in part through the autonomic nervous system<sup>12</sup> and its central connections. The VMC maintains a certain level of resting basal nervous tone through the sympathetic outflow which maintains arterial blood pressure at about twice the level it would be in the complete absence of sympathetic outflow from the VMC. On the other hand complete denervation of a vein does not produce a great decrease in venous pressure; nevertheless venous smooth muscle tone is modified by the CNS and autonomic nervous system. In general a decrease in sympathetic outflow results in a decrease in heart rate, a decrease in the force of myocardial contraction, relaxation of arteriolar and venous tone and in turn a decrease in arterial and venous blood pressure. On the other hand an increase in sympathetic outflow results in an increase in heart rate, an increase in the force and rate of myocardial contraction, augmented arteriolar and venous tone and in turn an increase in arterial and venous blood pressure.

The sympathetic outflow from the vasomotor center described above represents the efferent arc of the autonomic reflex pathways concerned with cardiovascular regulation. Afferent impulses reach the VMC from afferent sites scattered throughout the cardiovascular system, important ones being the pressor receptors in the aortic arch.

- petence blood volume and exercise J Clin Invest 25 937 1946
- 4 Burch G E and Hyman A Influence of a hot and humid environment upon cardiac output and work in normal man and in patients with chronic congestive heart failure at rest AM HEART J 53 605 1957
- 5 Burch G E A method for measuring venous tone in digital veins of intact man Evidence for increased digital venous tone in congestive heart failure Arch Intern Med 94 724 1954
- 6 Burch G E Evidence for increased venous tone in chronic congestive heart failure Arch Intern Med 111 740 1956
- 7 Clement H L and Shepherd J T Regulation of peripheral circulation during muscular exercise Progr Cardiovasc Dis 19 73 1956
- 8 Millard R W Higgins C H Franklin H and Vatner S F Regulation of the renal circulation during severe exercise in normal dogs and dogs with experimental heart failure Circ Res 31 651 1972
- 9 Starling E H Principles of Human Physiology London 1917 J & A Churchill Ltd p 1277
- 10 Duggan J J and Pitts R F Studies on diuretics I The site of action of mercurial diuretics J Clin Invest 29 365 1950
- 11 Pitts R F and Duggan J J Studies on diuretics II The relationship between glomerular filtration rate proximal tubular absorption of sodium and diuretic efficacy of mercurials J Clin Invest 29 370 1950
- 12 Leaf A and Couter W T Evidence that renal sodium excretion by normal human subjects is regulated by adrenal cortical activity J Clin Invest 28 1067 1949
- 13 Hughes D J Turner H H Moseley A J and Merrill A J Mechanisms of salt and water retention in heart failure Am J Med 7 249 1949
- 14 Davis J O and Freeman R H Mechanisms regulating renin release Physiol Rev 56 1 1976
- 15 Grollman A and Grollman E F Pharmacology and Therapeutics (7th Edition) Philadelphia 1970 Lea & Febiger pp 456-457
- 16 Burch G E León Galindo J and Cronvich J A New treatment for chronic intractable congestive heart failure AM HEART J 91 700 1966
- 17 Malaret G Quiroz A and Burch G E Venomotor reactions in the forearm veins of man Human Biol 32 135 1960
- 18 Folkow B Description of the myogenic hypothesis Circ Res (Suppl 1) 14 and 15 1964
- 19 Burch G E and Murtadha M A study of the venomotor tone in a short intact venous segment of the forearm of man AM HEART J 61 805 1956
- 20 Braunwald E Regulation of the circulation N Engl J Med 290 1124 1470 1974
- 21 Zeis R Nellis S H Longhurst J Lee G and Mason D T Abnormalities in the regional circulations accompanying congestive heart failure Progr Cardiovasc Dis 18 161 1975
- 22 Burch G E and DePasquale N P Methods for studying the influence of higher central nervous centers on the peripheral circulation of intact man AM HEART J 70 411 1965
- 23 Szekely F Venous pressure responses to exercise Preliminary report AM HEART J 22 660 1941
- 24 Jenkinson D McE Comparative physiology of sweating Br J Dermatol 88 197 1973
- 25 Best C H and Taylor N H The Physiological Basis of Medical Practice (8th ed) Baltimore 1966 The Williams & Wilkins Co p 1418
- 26 Kuno Y The Physiology of Human Perspiration London 1934 J & A Churchill Ltd p 207
- 27 Hurley B J and Shelley W B The Human Apocrine Sweat Gland in Health and Disease Springfield Illinois 1960 Charles C Thomas Publisher

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material."

myocardial contraction there is an increase in venous tone as well as in right atrial pressure'.<sup>1</sup> Thus, there is a rise in right ventricular filling pressure, and for each increment in filling pressure there is an increase in cardiac output. However, eventually a point is reached at which an increase in filling pressure is no longer associated with an increase in cardiac output and, indeed, may be associated with a decrease in cardiac output. Thus an increase in venous tone at first contributes to compensation but later may possibly contribute to decompensation.<sup>11</sup> The increase in venous tone in chronic congestive heart failure is initiated and maintained by increased sympathetic outflow from the VMC. The evidence for increased venous tone in chronic congestive heart failure is:

1. Static pressure (mean circulatory pressure) is higher in patients with congestive heart failure than in patients without congestive heart failure.

2. Sympathetic ganglionic blockade produces a greater decrease in venous pressure in patients with congestive heart failure than in patients without congestive heart failure.<sup>1</sup>

3. Digital rheoplethysmograms indicate that congestive heart failure is associated with marked increase in tone of the pre- and postcapillary blood vessels and that the postcapillary constriction tends to be greater than the precapillary constriction.

4. Exercise is associated with a much greater increase in venous pressure in patients with congestive heart failure than in normal patients.<sup>1</sup>

The increased sympathetic discharge associated with chronic congestive heart failure is probably also responsible, at least in part, for increased salt and water retention associated with the congestive heart failure. It should be mentioned that it is claimed that the decreased ability of the kidney to handle a sodium load in chronic congestive heart failure may appear before an increase in venous pressure. However, as already mentioned, systemic venous pressure may not reflect regional venous tone. The question of whether sodium and water retention precedes the increases in venous tone is unanswered.

### Hypothesis of neuropathophysiology of CHF

The clinical syndrome of congestive heart failure is to a large extent a functional disorder of

the central nervous system and peripheral nervous system ( $\alpha$  adrenergic and  $\beta$  adrenergic sympathetic nervous system). It is not primarily a disease of the central and sympathetic nervous systems but is secondary to a change in the function precipitated by the heart disease. The mechanism by which this generalized functional change in the nervous systems occurs is yet to be learned. The level of cardiac output itself does not trigger the central and sympathetic nervous system changes. The changes occur even when cardiac output at rest is no lower or even when it is higher than that of an individual sound asleep in bed at 3 o'clock in the morning. The cardiac circulatory (systemic and pulmonary), renal, hepatic and cerebral pathophysiologic manifestations of CHF reflect the altered CNS and sympathetic nervous system function. The state of function of the nervous systems in CHF is not a disease state. This functional state is a state that any normally functioning CNS and sympathetic nervous system would develop in any person with heart disease that progresses to the stage of CHF.

### Summary

Even though congestive heart failure is extremely common the mechanisms responsible for the clinical manifestations remain a puzzle. The central and autonomic (sympathetic) nervous systems are responsible for a large part of the clinical manifestations. The role of the nervous system in CHF is discussed briefly. It is evident that there are many gaps in knowledge that remain concerning the role of the central, peripheral and autonomic nervous systems in congestive heart failure.

The peripheral vascular constriction, increase in venous tone and pressure, tachycardia, sweating, dermal pallor and tension and anxiety in patients with CHF reflect generalized sympathetic nervous system activity and the influence of the central and autonomic nervous systems on the clinical syndrome of CHF.

### REFERENCES

1. Second National Conference on Cardiovascular Disease. The heart and circulation. Vol. 1. Washington D. C. 1964.
2. Burch G. E. A Primer of Congestive Heart Failure. Springfield, Illinois, 1964. Charles C. Thomas, Publisher.
3. Landis E. M., Brown F., Fauteux M. and Wise C. Central venous pressure in relation to cardiac com-

constriction) Possibly in keeping with this proposal is the recent observation of Cambridge Davey and Massingham<sup>7</sup> who found that unlike phenoxybenzamine which blocks both pre and post synaptic alpha adrenergic receptors prazosin appeared to inhibit the post synaptic adrenergic receptor selectively in rabbit pulmonary artery. Tritiated norepinephrine overflow during nerve stimulation a consequence of inhibition of the presynaptic adrenergic receptor<sup>8</sup> occurred following treatment with phenoxybenzamine but was not observed despite equally effective inhibition of artery contraction with prazosin.

It is believed that the effects of alpha adrenergic receptor stimulation are mediated by a decrease in adenylate cyclase activity and cyclic AMP concentration in the post synaptic neurone. Prazosin by virtue of its ability to inhibit phosphodiesterase activity might interfere with alpha adrenergic nerve function by preventing the fall in cyclic AMP which normally occurs following post synaptic alpha adrenergic receptor occupancy. The biochemical steps which link occupancy of the pre synaptic adrenergic receptor to its biologic action inhibition of norepinephrine release have not been elucidated. It seems reasonable to speculate that this effect might not be cyclic AMP mediated and might therefore be unaffected by prazosin.

Experimental evidence suggests that the hypotensive effect of prazosin is not mediated through effects on the central nervous system or by inhibition of beta adrenergic receptors.<sup>2</sup> Tachycardia and fall in blood pressure in response to isoproterenol are in fact enhanced by prior administration of prazosin in the rat.

#### Systemic hemodynamic and renal responses to prazosin in man

Cardiac output is either increased or remains unchanged when blood pressure is lowered with prazosin in patients with essential hypertension. Total peripheral resistance is significantly decreased. In a small series of normal subjects and in patients with severe congestive heart failure prazosin was found to decrease both forearm vascular (arteriolar) resistance and forearm venous tone. During passive head up tilt cardiac output falls and total peripheral resistance increases in hypertensive patients receiving prazosin although standing blood pressure is lower than supine blood pressure in patients receiving prazosin orthostatic hypoten-

sion is not commonly observed during chronic administration of prazosin = Renal blood flow (clearance of  $\beta$  aminohippurate) and glomerular filtration rate (inulin clearance or endogenous creatinine clearance) have been reported to be unchanged in patients receiving prazosin.<sup>10, 12</sup>

Several observers have noted that the hypotensive response to prazosin is not associated with tachycardia.<sup>2, 10, 13</sup> Plasma renin activity is not significantly increased in response to blood pressure lowering with prazosin.<sup>2, 10, 13, 14</sup> Experimentally it has been observed that unlike hydralazine or diazoxide intravenous administration of prazosin failed to elicit an increase in plasma renin activity in the dog.<sup>15, 16</sup>

The absence of tachycardia or increased renin release during prazosin administration contrasts sharply with changes in heart rate and plasma renin activity associated with administration of known vasodilator drugs such as hydralazine, diazoxide, nitroprusside and minoxidil. Tachycardia and increased renin release observed when arterial pressure is decreased by arteriolar vasodilators are generally attributed to reflex sympathetic stimulation. The failure to observe these sympathetically mediated responses during prazosin administration may be taken as evidence of the ability of prazosin to block sympathetic nerve stimulation. As noted above the major effect of prazosin on adrenergic nerve function appears to be interference with alpha adrenergic stimulation; the response of beta adrenergic receptors to the agonist isoproterenol was found to be enhanced by prazosin. Since reflex tachycardia and increased renin release are mediated by beta adrenergic receptors the failure to observe these responses during blood pressure lowering with prazosin cannot be attributed simply to inhibition of alpha adrenergic nerve function. Ganong<sup>17</sup> found that alpha adrenergic blockade resulted in increased renin release in the dog. Inhibition of central sympathetic discharge i.e. inhibition of both alpha and beta adrenergic function might provide a reasonable explanation for the absence of reflex increase in heart rate and renin release during prazosin administration but studies to date have failed to reveal evidence of a central site of action of prazosin. Cambridge Davey, and Massingham<sup>7</sup> found that prazosin selectively inhibits post synaptic alpha adrenergic receptor function leaving presynaptic receptors intact. It is conceivable that under conditions of selective post synaptic alpha adrenergic blockade norepi-

# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

## Prazosin

Jerome Lowenstein M D

John M Steele Jr, M D

New York N Y

Prazosin (Minipress, Pfizer), 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine hydrochloride, was approved by the Food and Drug Administration for the treatment of hypertension in 1976. Structurally it combines the 4-amino pyrimidine moiety found in cyclic AMP and the dimethoxy benzo moiety of papaverine, a recognized inhibitor of phosphodiesterase. Studies in rat heart and aorta demonstrate that prazosin is a more potent inhibitor of cyclic AMP hydrolysis than is either theophylline or hydralazine.<sup>1</sup> The drug is taken up rapidly by various tissues. Its plasma half-life is one to two hours but its hypotensive action is more prolonged presumably due to persistence of the drug at effective concentration at target sites. It is excreted largely as a glucuronide metabolite in stool and urine.<sup>2</sup>

Pharmacologic studies have suggested at least two different mechanisms responsible for the hypotensive effects of prazosin. Constantine and associates<sup>3</sup> reported that the intraarterial infusion of prazosin in the forelimb of the dog resulted in a dose dependent reduction in arteriolar resistance. The effect on vascular resistance was markedly attenuated by pretreatment with the ganglion blocking agent hexamethonium, but was not completely abolished as was the vasodilation induced by the alpha adrenergic antagonist, phentolamine. In contrast the vasodilatory action of diazoxide, a direct vasodilator, was unaffected by pretreatment with hexamethonium. Constantine and colleagues<sup>3</sup> concluded that a significant component of the hypotensive action of prazosin was attributable to direct smooth muscle relaxation.

While studies in the perfused forelimb suggest a direct vasodilator effect, studies in the intact animal indicate that the vasodilator effect is abolished by prior ganglionic blockade or alpha adrenergic blockade and make it appear more likely that the hypotensive action of prazosin is mediated predominantly by interference with alpha adrenergic stimulation of resistance vessels. Graham and co-workers<sup>4</sup> and Oates and colleagues<sup>5</sup> found that the hypotensive effect of prazosin was completely abolished by ganglionic blockade with pentolinium or alpha adrenergic blockade (phentolamine) in the anesthetized rat. Scivoletto and associates<sup>6</sup> found that the hypotensive effect of prazosin was abolished by alpha adrenergic blockade with ortho carboxy benzo seleninic acid in the dog. Further evidence that prazosin exerts a sympathetic blocking action comes from the observation that the decrease in vascular resistance in the limb of the rat perfused intraarterially with prazosin is dependent on the presence of intact sympathetic innervation of the limb.<sup>4</sup> Further, prazosin causes epinephrine reversal,<sup>7</sup> an action which is generally taken as evidence that a drug acts as an alpha adrenergic antagonist. Finally prazosin decreases the pressor effects of infused norepinephrine,<sup>8</sup> but does not block the pressor effect of angiotensin II,<sup>9</sup> suggesting a specific interference with alpha adrenergic stimulation. Unlike phentolamine which appears to function as a competitive inhibitor of norepinephrine at the alpha adrenergic receptor, prazosin does not protect alpha adrenergic receptors against irreversible inhibition by phenoxylbenzamine. This finding led Constantine and colleagues<sup>3</sup> to suggest that prazosin in contrast to phentolamine does not act by competing for occupancy of alpha adrenergic receptor sites but rather by affecting some subsequent step in the sequence linking receptor occupancy to target tissue effect (vaso-

From the Renal Section, New York University School of Medicine.  
Received for publication October 10, 1977.

Reprint requests: Jerome Lowenstein M.D., Renal Section, New York University School of Medicine, 550 First Ave., New York, N.Y. 10016.

prazosin. In many instances patients who experienced hypotension at the initiation of prazosin treatment tolerated further treatment with even greater doses subsequently.

The occurrence of the first dose phenomenon in some patients does not appear to reflect greater plasma concentrations of prazosin. It has been suggested that the frequency of occurrence and the severity of the first dose phenomenon can be minimized by administration of a small dose initially and by taking the drug with meals rather than in the fasting state. Dietary sodium restriction appears to predispose to the occurrence of severe initial orthostatic hypotension.

In summary, prazosin is an orally administered antihypertensive drug which appears to act as both a direct vasodilator and a sympathetic blocking agent. It is unique among vasodilator drugs in that reflex tachycardia and increased renin release are not seen with blood pressure lowering. It appears to be effective in mild, moderate and severe hypertension. As with most other antihypertensive drugs, significant synergism with diuretics has been observed. While orthostatic hypotension is not common, acute hemodynamic collapse termed the first dose phenomenon has been observed in some patients at the onset of treatment with this drug but may be avoided if therapy is initiated with small doses.

## REFERENCES

- Hess H J. Prazosin: Biochemistry and structure activity studies. *Postgrad Med (Suppl)* 9: November 1975.
- Constantine J W, McShane W A, Scrabine A and Hess H J. Analysis of the hypotensive action of prazosin in Hypertension: Mechanisms and management. Onesti, G Kim K F and Moyer J H Editors. New York 1973 Grune & Stratton Inc p 429.
- Graham R M, Oates H F, Stoker L M and Stokes G S. Alpha blocking action of the antihypertensive agent prazosin. *J Pharmacol Exp Ther* 201:747 1977.
- Oates H F, Graham R M, Stoker L M and Stokes G S. Hemodynamic effects of prazosin. *Arch Int Pharmacodyn Ther* 224:30-39 1976.
- Scofield R L, Toledo A J O, Gomes Da Silva A C and Bigro B. Mechanism of the hypotensive effect of prazosin. *Arch Int Pharmacodyn Ther* 223:333 1976.
- Wood A J, Phelan E L and Simpson F B. Cardiovascular effects of prazosin in normotensive and genetically hypertensive rats. *Clin Pharmacol Phys* 2:797 1975.
- Cambridge D, Davey M J and Massingham R. Prazosin: a selective antagonist of post synaptic  $\alpha_1$  adrenoceptors. *Br J Pharmacol* 59:514 P 1977.
- Langner S Z, Enero M A, Adler-Graschinsky E, Dubocovich H L and Celucha S M. Presynaptic

regulatory mechanisms for noradrenaline release by nerve stimulation in Central action of drugs in blood pressure regulation. Davis D H and Redd J L. Editors. New York 1975 Pitman p 133.

- Lund-Johansen P. Hemodynamic changes at rest and during exercise in long term prazosin therapy for essential hypertension. *Postgrad Med (Suppl 4)* November 1977.
- Kosby M C, Mickle D, Bourgoigne J and Blaufox M D. Physiologic evaluation of a new antihypertensive agent prazosin. *HC1 Circulation* 55:533 1977.
- Awan N A, Miller R R, Maxwell K S and Mason D T. Effects of prazosin on forearm resistance and capacitance vessels. *Clin Pharmacol Ther* 22:79 1977.
- Maxwell M H. Effects of prazosin on renal function and fluid-electrolyte metabolism. *Postgrad Med (Suppl 36)* November 1975.
- Lowenstein J. Combination drug therapy of hypertension. *Excerpta Med in Proceedings of the International Conference on Arterial Hypertension Caracas, Venezuela Sept 1976*.
- Hayes J M, Graham R M, O'Connell B P, Muir M R, Spiers E and Humphrey T J. Experience with prazosin in the treatment of patients with severe hypertension. *Med J Aust* 1:562 1976.
- Stokes G S and Weber M A. Prazosin: Preliminary report and comparative studies with other antihypertensive agents. *Br Med J* 11:298 1974.
- Belli P, Wood A J and Simpson F B. Effects of prazosin in patients with hypertension. *Clin Pharmacol Ther* 20:133, 1976.
- Graham R M, Muir M R, and Hayes J M. Differing effects of vasodilator drugs prazosin and diazoxide on plasma renin activity in the dog. *Clin Exp Pharmacol Physiol* 3:173 1976.
- Massingham R and Hayden M L. Comparison of effects of prazosin and hydralazine on blood pressure, heart rate and plasma renin activity in conscious renal hypertensive dogs. *Eur J Pharmacol* 30:121 1975.
- Ganong W F. Effects of sympathetic activity and ACTH on renin and aldosterone secretion. In: *Hypertension* 72, Genest J, and Kow E. editors. Berlin Heidelberg New York 1972 Springer Verlag p 4.
- Bradley W F, Hoffman F G, Hutchison J C, Kalams Z and Waldron S L. Comparison of prazosin and methyldopa in mild to moderate hypertension: a multicenter cooperative study. *Ther Res* 21:78 1977.
- Bloom D S, Rosenhardt C and Kramer R. Clinical evaluation of prazosin as the sole agent for the treatment of hypertension. A double blind cross-over study with methyldopa. *Curr Ther Res* 18:144 1975.
- Cohen B M. Prazosin hydrochloride (CP 12,139) an oral antihypertensive agent: preliminary clinical observations in ambulatory patients. *J Clin Pharmacol* 10:408 1970.
- Rouger M, Lahon M F S, Clin J, A R. Prazosin—a new antihypertensive agent. *Br J Clin Pract* 28:790 1974.
- Hus A S P, Macdonald J M, Myers J B, Fang P and Kincaid Smith P. Studies with prazosin—A new effective hypotensive agent. *Med J Aust* 2:5 1977.
- Curtis J R and Bateman F J A. Use of prazosin in management of hypertension in patients with chronic renal failure and in renal transplant recipients. *Br Med J* 4:432, 1975.
- Miller R R, Awan N A, Maxwell K S, and Mason D T. Sustained reduction of cardiac impedance and preload in congestive heart failure with the antihypertensive vasodilator prazosin. *N Engl J Med* 297:303 1977.



nephrine release from presynaptic vesicles can be inhibited by the intact presynaptic receptors and thereby limit the 'overflow' of norepinephrine responsible for recruitment of closely associated beta adrenergic receptors during reflex sympathetic stimulation

### Clinical application of prazosin

In double blind cross over or controlled studies, several groups<sup>20-22</sup> have reported that prazosin 1 mg given three times daily was as effective as methyldopa 750 mg daily in lowering blood pressure of patients with mild to moderate hypertension

Bloom, Rosendorff and Kramer<sup>21</sup> compared prazosin and methyldopa in a double blind cross over study in 30 patients with mild and moderate hypertension. The dosage of each drug was increased as needed to attain a standing diastolic pressure below 100 mm Hg. A satisfactory blood pressure response was achieved in 16 of 25 trials with prazosin (mean daily dose 9.5 mg) and 17 of 27 trials with methyldopa (mean daily dose 1.325 mg). The incidence of side effects was comparable with the two drugs.

In a multicenter double blind study Bradley and colleagues<sup>20</sup> found comparable blood pressure reduction in patients receiving prazosin (1 mg three times daily) and methyldopa (250 mg three times daily). When drug dosage was increased to attain optimal blood pressure control, reduction of standing diastolic pressure below 100 mm Hg was observed in 14 of 19 (73.7 per cent) patients receiving prazosin (average dose 8.5 mg/day) as compared with nine of 19 patients receiving methyldopa (average dose 1.183 mg/day).

In a double blind cross over study comparing prazosin and hydralazine in patients receiving diuretics and/or beta blocking agents, Hua and associates<sup>22</sup> found that 1 mg of prazosin was roughly equivalent to 20 mg of hydralazine in potency but noted a significantly lower incidence of side effects requiring discontinuation of therapy with prazosin.

The blood pressure response to prazosin was enhanced by concomitant administration of a thiazide diuretic in several controlled studies.<sup>22-25</sup> Cohen<sup>22</sup> found that the blood pressure response to the combination of prazosin with a thiazide diuretic (polythiazide) was significantly greater than that to either drug given alone. Rougier and co-workers<sup>23</sup> found that diastolic pressure fell below 100 mm Hg when thiazide diuretic was

administered together with prazosin in 30 of 35 patients who had failed to respond to prazosin alone. The synergistic effect of prazosin and thiazide diuretics is generally most striking in patients with more severe hypertension or higher control diastolic blood pressure. Although no controlled studies have yet been reported data presented by several groups<sup>21, 22</sup> indicate further lowering of blood pressure when prazosin was added to antihypertensive regimens including propranolol, clonidine, methyldopa and hydralazine singly or in combination.

Prazosin has been reported to be effective in lowering the blood pressure of patients with moderate and even advanced renal failure<sup>26</sup> without adverse effect on residual renal function. The observed decreases in forearm vascular resistance and venous tone<sup>27</sup> and the absence of tachycardia have led some investigators to suggest that prazosin might be effective in the treatment of intractable congestive heart failure by lowering preload and impedance.<sup>28</sup>

### Adverse effects

Side effects of prazosin include dizziness, fatigue, weakness, palpitations and headache. In most reported instances these side effects have not been so severe as to require discontinuing the drug. It appears that the occurrence of side effects of prazosin and their severity are less than that observed with methyldopa. Laboratory abnormalities have been minor and inconsistent. Positive Coombs' tests and drug induced lupus erythematosus have not been observed.<sup>29</sup>

The most troublesome adverse effect of prazosin has been termed the 'first dose phenomenon'. In various reports from two to 16 per cent of patients given an initial dose of prazosin have developed severe orthostatic hypotension, lightheadedness, dizziness, weakness or palpitations.<sup>30</sup> These responses are almost invariably seen at the initiation of prazosin treatment and in most reported instances have followed the administration of 2 mg of the drug. In one series<sup>31</sup> only two of seven patients who had experienced this first dose response when given 2 mg of prazosin experienced adverse effects, limited to mild dizziness when rechallenged with 0.5 mg of

*Lund-Johansen described one patient who developed a skin rash considered to be that of lupus erythematosus after 10 months of prazosin treatment. Fever and joint pain occurred four weeks later following withdrawal of the drug. The results of serologic studies (antinuclear antibodies, LE preparation) were not given.*

tuberculosis—none causes the valvular changes described in psittacosis. Thus, if an infective agent provides the link between bird contact and valve disease it is probably *Chlamydia psittaci*.

The concept of viral valvular disease suffers from a lack of evidence of past infection with cardiotropic viruses in patients with chronic valve lesions. The fortuitous epidemiology of psittacosis provides indirect but suggestive evidence in the case of *Chlamydia psittaci*. Consequently in one respect at least it is more suitable for study than for example the enteroviruses. Further investigation is now indicated to clarify the relationship between *Chlamydia psittaci* and valvular heart disease. This might take the form of

- 1 Follow up studies of proven cases of psittacosis
- 2 An investigation of the incidence of valvular disease in at risk groups of the population such as veterinary surgeons.
- 3 Studies of cardiac involvement in experimental models

Christopher Ward MD MRCP  
Cardiothoracic Unit  
Northern General Hospital  
Sheffield S6 7AU  
England

## REFERENCES

- 1 Ward C Virus valvular heart disease *Am Heart J* 90:804 1915
- 2 Finland M Parker F Barnes M W and Joffe L S Acute myocarditis in influenza A infections *Am J Med Sci* 209:455 1945
- 3 Ludden T E and Edwards J E Polymyositis An anatomical study of thirty five cases and review of the literature *Am J Pathol* 25:357 1949
- 4 Tatter D Gerard P W Wang C L and Pearson H E Fatal varicella pancarditis in a child *Am J Dis Child* 105:66 1964
- 5 Roberts W C and Fox S M Mumps of the heart *Circulation* 32:347 1965
- 6 Babb J M Stoneman M R and Stern H Myocarditis and group caused by Coxsackie virus type B5 *Arch Dis Child* 36:551 1961
- 7 Saman G S Krompotic E and Siodki S J Adult heart disease due to Coxsackie virus B infection *Medicine* 47:133 1968
- 8 Smith W G Adult heart disease due to Coxsackie virus group B *Br Heart J* 28:204 1966
- 9 Koontz C H and Ray C G The role of Coxsackie group B virus infections in sporadic myocarditis *Am Heart J* 82:750 1971
- 10 Polayes H and Lederer M Psittacosis with results of postmortem examination in a case including studies of the spinal cord *Arch Intern Med* 49:253 1932
- 11 Jannach J H Myocarditis in infancy with inclusions characteristic of psittacosis, *Am J Dis Child* 96:734 1958
- 12 Dymock I W, Lawson J M MacLennan W J and Ross C A J Myocarditis associated with psittacosis *Br J Clin Pathol* 24:1971
- 13 Schofte A J Patho anatomic anomalies in psittacosis, *Nederlandsche Tijdschrift voor Geneeskunde* 74:2741 1930
- 14 Grist N H and McLean C Infections by organisms of the psittacosis lymphogranuloma group in the West of Scotland *Br Med J* 2:21 1964
- 15 Levison H A Guthrie W Ward C, Green H M, Robertson P G C Infective endocarditis as part of psittacosis, *Lancet* 2:844 1971
- 16 Burkhead J H and Apostolov K Endocarditis caused by a psittacosis agent *Br Heart J* 36:728 1974
- 17 Ward C, Ward A M Cooper D and Sagar H Insidious endocarditis caused by chlamydia psittaci, *Br Med J* 4:734 1975
- 18 Anderson J P Ornithosis in Somerset: Experience in the south Somerset clinical area 1964-71 *Postgrad Med J* 49:333 1973
- 19 Ward C Hildinger A L Morrissey R A and Birgh J P Psittacosis-lymphogranuloma venereum virus anti bodies in man: experience with thirty seven persons with respiratory disease having significantly high antibody titres *JAMA* 155:1146 1954
- 20 Ward C, and Ward A M Acquired valvular heart disease in patients who keep pet birds *Lancet* 2:734 1974
- 21 Bousson H Diseases of man acquired from his pets, London 1967 William Heinemann Medical Books Ltd

## On the significance of an abnormal P-terminal force in Lead V<sub>1</sub>

Left atrial enlargement produces a broad (0.12 second or greater) and bifid (interpeak interval > 0.04 second) P wave on the ECG. A broad P wave may also be caused by an intratrial conduction delay and hence this abnormality is not specific for left atrial enlargement. An abnormal P terminal force in Lead V<sub>1</sub> (PTF V<sub>1</sub>) is defined as a negative P in Lead V<sub>1</sub> the product of the depth (in mm) and the width (in second) of which is -0.04 mm second or less. An abnormal PTF V<sub>1</sub> is a useful sign of left atrial hypertension e.g. in acute myocardial infarction. A recent echocardiographic study has shown that acute left atrial hypertension does not usually result in left atrial enlargement. Conversely left atrial enlargement may occasionally be present without an increase

in left atrial pressure. Thus an abnormal PTF V<sub>1</sub> may be a sign of left atrial enlargement and/or left atrial hypertension. When an abnormal PTF V<sub>1</sub> is seen in a patient with acute myocardial infarction the P wave often reverts to normal when the left atrial pressure returns to normal levels. Thus this electrocardiographic sign is useful in following the course of patients with acute myocardial infarction.

Severe right atrial hypertension may sometimes produce an abnormal PTF V<sub>1</sub>. In this situation the physical examination and the ECG usually reveal evidence of right atrial enlargement (Tall P waves > 2.5 mm) and/or right ventricular hypertrophy. A P vectorcardiogram will show a clockwise loop in right atrial enlargement with abnormal PTF V<sub>1</sub> whereas in

## "Rheumatic" heart disease, psittacosis and the importance of epidemiology

The evidence which supports the concept of viral valvular disease is fragmented several viruses are suspected of involvement but significant gaps exist in the chain of evidence which is quoted in support of an etiological connection. The study of viral valvular disease may be facilitated if attention is focused first on identifying these gaps—and then on the systematic investigation of specific organisms which appear most likely to provide the missing answers.

A connection between rheumatic fever and chronic valvular disease was substantiated by

1 Clinical evidence of valve lesions in patients with acute rheumatic fever

2 Postmortem demonstration of valve damage in patients dying from acute rheumatic fever

3 Follow up of patients recovered from acute rheumatic fever showing the development of chronic valve disease

4 Retrospective studies indicating that many patients with chronic valvular disease have a rheumatic history

When the evidence for virus valvular disease is assessed on this basis a major deficiency becomes apparent. Evidence under paragraphs Nos 1 and 2 above has been established for several viruses and follow up studies comparable to those in paragraph No 3 are in progress. However evidence under the fourth heading which is axiomatic if the proposed relationship is correct is more elusive. It is difficult if not impossible to detect long past infection with most common viruses and yet the lack of such a link vis a vis viruses and valvular disease is a major weakness in the argument of those who propose that such a relationship exists. Consequently any virus infection which not only causes acute valvular damage but for which there is also evidence suggesting its past occurrence in patients with chronic valve disease merits special attention. One organism which goes some way towards fulfilling these criteria *Chlamydia psittaci* the causative agent of psittacosis has been largely ignored.

### Reports of valvular or endocardial damage in psittacosis

Descriptions of cardiac involvement in psittacosis are rare. However in eight of 12 reports valvular or endocardial damage of one kind or another was noted. Polajec and Lederer described postmortem findings in a 51 year old housewife who died from cardiorespiratory failure 11 days after hospitalization because of a cough and influenza. Macroscopic and microscopic changes were present in the aortic mitral and tricuspid valves and included marked subendocardial deposits of fibrin in the middle aortic cusp. Jannach described an 18-month-old child who died in congestive heart failure. Numerous translucent glistening elevations 2 mm in diameter were present on the mitral valve cusps. Discrete collections of lymphocytes and monocytes

were found beneath the mitral valve endocardium. The infiltration was prominent in the anterior papillary muscle and was associated with endothelial proliferation. Dymock and colleagues<sup>10</sup> reported findings from a 13-year old boy who had rapidly progressive cardiac failure. Subendocardial accumulations of lymphocytes and monocytes were seen. The findings described by Jannach<sup>11</sup> are particularly significant for they are reminiscent of the characteristic macroscopic appearances of acute rheumatic valvulitis. Valvular damage due to *Chlamydia psittaci* in the form of infective endocarditis has also been reported. The patients described by Schöle and by Grist and McLean<sup>12</sup> were probably examples of this entity. Better documented cases have been published more recently.<sup>13</sup> Diagnosis was based on histochemical staining, electron microscopy,<sup>14</sup> or immunofluorescent staining combined with serology. Pre-existing valve disease was not always present and in one case the illness was subclinical. These reports are sparse but show that in most published cases of cardiac involvement in psittacosis the endocardium was affected.

### Epidemiological studies

Three epidemiological features of psittacosis are relevant to this discussion.

1 Infection with *Chlamydia psittaci* is far more common than official figures suggest and often occurs as a mild febrile illness.<sup>15</sup>

2 Most victims of overt psittacosis have a history of bird contact.

3 Occupational contact with birds—by veterinary surgeons, pet shop owners or poultry workers—increases the risk of infection.<sup>16</sup>

Many cases of psittacosis can be traced to pet birds and so it follows that as a group people who keep these pets have a greater chance of contracting psittacosis than people who do not. Epidemiological studies have demonstrated a connection between bird contact and valvular heart disease.<sup>17</sup> Twelve patients with valvular disease were divided into those with and those without a rheumatic history. It was found that a history of having kept pet birds was significantly more common in those who had not had rheumatic fever (63 per cent as opposed to 45 per cent,  $\chi^2 = 7.73$ ,  $p < 0.01$ ). Furthermore using the same grouping of patients those with no rheumatic history more often developed symptoms of heart disease in the 15 years immediately following first contact with birds (46 per cent as opposed to 27 per cent,  $\chi^2 = 4.31$ ,  $p < 0.05$ ). The findings relate to bird contact—not to psittacosis. However of the infections which have occasionally been acquired by man from birds—St. Louis encephalitis, Japanese B encephalitis, Murray Valley encephalitis, West Nile fever, Newcastle disease, poxvirus, salmonella and avian

tuberculosis—none causes the valvular changes described in psittacosis. Thus if an infective agent provides the link between bird contact and valve disease it is probably *Chlamydia psittaci*.

The concept of viral valvular disease suffers from a lack of evidence of past infection with cardiotropic viruses in patients with chronic valve lesions. The fortuitous epidemiology of psittacosis provides indirect but suggestive evidence in the case of *Chlamydia psittaci*. Consequently in one respect at least it is more suitable for study than for example the enteroviruses. Further investigation is now indicated to clarify the relationship between *Chlamydia psittaci* and valvular heart disease. This might take the form of

- 1 Follow up studies of proven cases of psittacosis
- 2 An investigation of the incidence of valvular disease in at risk groups of the population such as veterinary surgeons.
- 3 Studies of cardiac involvement in experimental models

Christopher Ward MD MRCP  
Cardiothoracic Unit  
Northern General Hospital  
Sheffield S5 7AU  
England

## REFERENCES

- 1 Ward C Virus valvular heart disease *Am Heart J* 90:404 1975
- 2 Finland M Parker F Barnes M W and Johlfie L S Acute myocarditis in influenza A infections *Am J Med* 40: 209-215 1945
- 3 Ludden T E, and Edwards J E Polymyositis: An anatomical study of thirty five cases and review of the literature *Am J Pathol* 25:307 1949
- 4 Tatter D Gerard P W, Wang C I and Pearson H E Fatal valvular pancarditis in a child *Am J Dis Child* 108:111 1961
- 5 Roberts W C and Fox S M Mumps of the heart *Circulation* 32:34 1965
- 6 Babb J M Bloneman M E R and Stern H Myocarditis and group caused by Coxsackie virus type B5 *Arch Dis Child* 36:551 1961

- 7 Samara G S Krompotic E and Siodki S J Adult heart disease due to Coxsackie virus B infection *Medicine* 47:133 1968
- 8 Smith W G Adult heart disease due to Coxsackie virus group B *Br Heart J* 28:204 1966
- 9 Koontz C H, and Ray C G The role of Coxsackie group II virus infections in sporadic myopericarditis, *Am Heart J* 82:750 1971
- 10 Polavics S H and Lederer M Psittacosis with results of postmortem examination in a case including studies of the spinal cord *Arch Intern Med* 49:253 1937
- 11 Jannach J R Myocarditis in infancy with inclusions characteristic of psittacosis, *Am J Dis Child* 96:734 1956
- 12 Dymock I W Lawson J M MacLennan W J and Ross C A C Myocarditis associated with psittacosis *Br J Clin Pract* 25:240 1971
- 13 Scholte A J Patho-anatomic anomalies in psittacosis *Nederlandsche Tijdschrift voor Geneeskunde* 74:2741 1930
- 14 Grist M R and McLean C Infections by organisms of the psittacosis lymphogranuloma group in the West of Scotland *Br Med J* 2:21 1964
- 15 Levinson D A, Guthrie W, Ward C Green D M Robertson P G C Infective endocarditis as part of psittacosis, *Lancet* 2:844 1971
- 16 Kirkhead J S, and Apostolev K Endocarditis caused by a psittacosis agent *Br Heart J* 36:728 1974
- 17 Ward C, Ward A M Cooper D and Sagar H Insidious endocarditis caused by chlamydia psittaci, *Br Med J* 4:734 1955
- 18 Anderson J P Ornithosis in Somerset: Experience in the south Somerset clinical area 1964-71 *Postgrad Med J* 49:333 1973
- 19 Ward C, Hildinger A L Morrissey R A and Burgh J P Psittacosis—lymphogranuloma venereum virus antibodies in man: experience with thirty seven persons with respiratory disease having significantly high antibody titres, *JAMA* 155:1146 1954
- 20 Ward C and Ward A M Acquired valvular heart disease in patients who keep pet birds *Lancet* 2:734 1974
- 21 Buser B Diseases of man acquired from his pets *London 1967 William Heinemann Medical Books Ltd*

## On the significance of an abnormal P-terminal force in Lead V<sub>1</sub>

Left atrial enlargement produces a broad (0.12 second or greater) and bifid (interpeak interval > 0.04 second) P wave on the ECG. A broad P wave may also be caused by an intratrial conduction delay and hence this abnormality is not specific for left atrial enlargement. An abnormal P terminal force in Lead V<sub>1</sub> (PTF V<sub>1</sub>) is defined as a negative P in Lead V<sub>1</sub> the product of the depth (in mm) and the width (in seconds) of which is -0.04 mm second or less. An abnormal PTF V<sub>1</sub> is a useful sign of left atrial hypertension e.g. in acute myocardial infarction. A recent echocardiographic study has shown that acute left atrial hypertension does not usually result in left atrial enlargement. Conversely left atrial enlargement may occasionally be present without an increase

in left atrial pressure. Thus an abnormal PTF V<sub>1</sub> may be a sign of left atrial enlargement and/or left atrial hypertension. When an abnormal PTF V<sub>1</sub> is seen in a patient with acute myocardial infarction the P wave often reverts to normal when the left atrial pressure returns to normal levels. Thus this electrocardiographic sign is useful in following the course of patients with acute myocardial infarction.

Severe right atrial hypertension may sometimes produce an abnormal PTF V<sub>1</sub>. In this situation the physical examination and the ECG usually reveal evidence of right atrial enlargement (Tall P waves > 2.5 mm) and/or right ventricular hypertrophy. A vectorcardiogram will show a clockwise loop in right atrial enlargement with abnormal PTF V<sub>1</sub> whereas in

## "Rheumatic" heart disease, psittacosis and the importance of epidemiology

The evidence which supports the concept of viral valvular disease is fragmentary: several viruses are suspected of involvement but significant gaps exist in the chain of evidence which is quoted in support of an etiological connection. The study of viral valvular disease may be facilitated if attention is focused first on identifying these gaps—and then on the systematic investigation of specific organisms which appear most likely to provide the missing answers.

A connection between rheumatic fever and chronic valvular disease was substantiated by

1 Clinical evidence of valve lesions in patients with acute rheumatic fever

2 Postmortem demonstration of valve damage in patients dying from acute rheumatic fever

3 Follow up of patients recovered from acute rheumatic fever showing the development of chronic valve disease

4 Retrospective studies indicating that many patients with chronic valvular disease have a rheumatic history

When the evidence for virus valvular disease is assessed on this basis a major deficiency becomes apparent. Evidence under paragraphs Nos 1 and 2 above has been established for several viruses, and follow up studies comparable to those in paragraph No 3 are in progress. However, evidence under the fourth heading which is a *sine qua non* if the proposed relationship is correct is more elusive. It is difficult if not impossible to detect long past infection with most common viruses, and yet the lack of such a link vis à vis viruses and valvular disease is a major weakness in the argument of those who propose that such a relationship exists. Consequently any virus infection which not only causes acute valvular damage but for which there is also evidence suggesting its past occurrence in patients with chronic valve disease merits special attention. One organism which goes some way towards fulfilling these criteria, *Chlamydia psittaci*, the causative agent of psittacosis, has been largely ignored.

### Reports of valvular or endocardial damage in psittacosis

Descriptions of cardiac involvement in psittacosis are rare. However, in eight of 12 reports valvular or endocardial damage of one kind or another was noted. Polajec and Lederer described postmortem findings in a 51-year-old housewife who died from cardiorespiratory failure 11 days after hospitalization because of a cough and influenza. Macroscopic and microscopic changes were present in the aortic mitral and tricuspid valves and included marked subendocardial deposits of fibrin in the middle aortic cusp. Jannach<sup>1</sup> described an 18-month-old child who died in congestive heart failure. Numerous translucent glistening elevations 2 mm in diameter were present on the mitral valve cusps. Discrete collections of lymphocytes and monocytes

were found beneath the mitral valve endocardium. The infiltration was prominent in the anterior papillary muscle and was associated with endothelial proliferation. Divick and colleagues<sup>2</sup> reported findings from a 13-year-old boy who had rapidly progressive cardiac failure. Subendocardial accumulations of lymphocytes and monocytes were seen. The findings described by Jannach are particularly significant for they are reminiscent of the characteristic macroscopic appearances of acute rheumatic valvulitis. Valvular damage due to *Chlamydia psittaci* in the form of infective endocarditis has also been reported. The patients described by Schö<sup>3</sup> and by Grist and McLean<sup>4</sup> were probably examples of the entity. Better documented cases have been published more recently.<sup>5</sup> Diagnosis was based on histochemical staining, electron microscopy or immunofluorescent staining combined with serology. Pre-existing valve disease was not always present and in one case the illness was subclinical. These reports are sparse but show that in most published cases of cardiac involvement in psittacosis the endocardium was affected.

### Epidemiological studies

Three epidemiological features of psittacosis are relevant to this discussion.

1 Infection with *Chlamydia psittaci* is far more common than official figures suggest and often occurs as a mild febrile illness.

2 Most victims of overt psittacosis have a history of bird contact.

3 Occupational contact with birds—by veterinary surgeons, pet shop owners or poultry workers—increases the risk of infection.

Many cases of psittacosis can be traced to pet birds and so it follows that as a group people who keep these pets have a greater chance of contracting psittacosis than people who do not. Epidemiological studies have demonstrated a connection between bird contact and valvular heart disease.<sup>6</sup> When patients with valvular disease were divided into those with and those without a rheumatic history it was found that a history of having kept pet birds was significantly more common in those who had not had rheumatic fever (63 per cent as opposed to 45 per cent,  $\chi^2 = 7.73$ ,  $p < 0.01$ ). Furthermore, using the same grouping of patients those with no rheumatic history more often developed symptoms of heart disease in the 15 years immediately following first contact with birds (46 per cent as opposed to 27 per cent,  $\chi^2 = 4.34$ ,  $p < 0.05$ ). The findings relate to bird contact—not to psittacosis. However, of the infections which have occasionally been acquired by man from birds—St. Louis encephalitis, Japanese B encephalitis, Murray Valley encephalitis, West Nile fever, Newcastle disease, poliomyelitis, salmonella and avian

tuberculosis—none causes the valvular changes described in psittacosis. Thus, if an infective agent provides the link between bird contact and valve disease it is probably *Chlamydia psittaci*.

The concept of viral valvular disease suffers from a lack of evidence of past infection with cardiotropic viruses in patients with chronic valve lesions. The fortuitous epidemiology of psittacosis provides indirect but suggestive evidence in the case of *Chlamydia psittaci*. Consequently in one respect at least it is more suitable for study than for example the enteroviruses. Further investigation is now indicated to clarify the relationship between *Chlamydia psittaci* and valvular heart disease. This might take the form of

- 1 Follow up studies of proven cases of psittacosis
- 2 An investigation of the incidence of valvular disease in at risk groups of the population such as veterinary surgeons.
- 3 Studies of cardiac involvement in experimental models

Christopher Ward M.D. M.R.C.P.  
Cardiothoracic Unit  
Northern General Hospital  
Sheffield S5 7AU  
England

## REFERENCES

- 1 Ward C Virus valvular heart disease *AM HEART J* 80:804 1975
- 2 Finland M, Parker F, Barnes M W., and Johffe L S Acute myocarditis in influenza A infections *Am J Med Sci* 209:455 1945
- 3 Ludden T ■ and Edwards J E Polymyositis: An anatomical study of thirty five cases and review of the literature *Am J Pathol* 25:357 1949
- 4 Tetter D, Gerard P W, Wang C L, and Pearson H E Fatal varicella pancarditis in a child *Am J Dis Child* 108:88 1964
- 5 Roberts W C and Fox S M Mumps of the heart *Circulation* 32:347 1965
- 6 Babb J M, Stoneman M E H and Stern H Myocarditis and group caused by Coxsackie virus type B5 *Arch Dis Child* 35:551 1961

- 7 Samant, G S, Krumpoltz E and Slodki, S J Adult heart disease due to Coxsackie virus B infection *Medicine* 47:133 1968
- 8 Smith, W G Adult heart disease due to Coxsackie virus group B *Br Heart J* 28:204 1966
- 9 Koontz C H and Ray C G The role of Coxsackie group B virus infections in sporadic myocarditis, *AM HEART J* 82:750 1971
- 10 Polayes S H and Lederer M Psittacosis with results of postmortem examination in a case including studies of the spinal cord *Arch Intern Med* 49:253 1937
- 11 Jannach, J R Myocarditis in infancy with inclusions characteristic of psittacosis, *Am J Dis Child* 88:734 1958
- 12 Dymock I W, Lawson J M, MacLennan W J and Rosa, C A C Myocarditis associated with psittacosis *Br J Clin Pract* 28:240 1971
- 13 Scholte A J Patho-anatomic anomalies in psittacosis *Nederlandsche Tijdschrift voor Geneeskunde* 74:741 1930
- 14 Grant N R and McLean C Infections by organisms of the psittacosis lymphogranuloma group in the West of Scotland *Br Med J* 2:21 1964
- 15 Levinson D A, Guthrie W, Ward C., Green D M, Robertson P ■ C Infective endocarditis as part of psittacosis *Lancet* 2:844 1971
- 16 Burkhead J S and Apostolov K Endocarditis caused by a psittacosis agent *Br Heart J* 38:728 1974
- 17 Ward C, Ward A M, Cooper D., and Sagar H Insidious endocarditis caused by chlamydia psittaci, *Br Med J* 4:734 1975
- 18 Anderson J P Ornithosis in Somerset: Experience in the south Somerset clinical area 1964-71 *Postgrad Med J* 49:533 1973
- 19 Ward C, Hildinger A L, Morrison R A and Burgh J P Psittacosis-lymphogranuloma venereum virus antibodies in man: experience with thirty seven persons with respiratory disease having significantly high antibody titres *JAMA* 165:1146 1954
- 20 Ward C and Ward A M Acquired valvular heart disease in patients who keep pet birds, *Lancet* 2:734 1974
- 21 Buseru B Diseases of man acquired from his pets *London, 1967 William Heinemann Medical Books Ltd*

## On the significance of an abnormal P-terminal force in Lead V<sub>1</sub>

Left atrial enlargement produces a broad (0.12 second or greater) and bifid (interpeak interval > 0.04 second) P wave on the ECG. A broad P wave may also be caused by an intratrial conduction delay and hence this abnormality is not specific for left atrial enlargement. An abnormal P terminal force in Lead V<sub>1</sub> (PTF V<sub>1</sub>) is defined as a negative P in Lead V<sub>1</sub> the product of the depth (in mm.) and the width (in second) of which is < 0.01 mm second or less. An abnormal PTF V<sub>1</sub> is a useful sign of left atrial hypertension e.g. in acute myocardial infarction. A recent echocardiographic study has shown that acute left atrial hypertension does not usually result in left atrial enlargement. Conversely left atrial enlargement may occasionally be present without an increase

in left atrial pressure. Thus an abnormal PTF V<sub>1</sub> may be a sign of left atrial enlargement and/or left atrial hypertension. When an abnormal PTF V<sub>1</sub> is seen in a patient with acute myocardial infarction the P wave often reverts to normal when the left atrial pressure returns to normal levels. Thus this electrocardiographic sign is useful in following the course of patients with acute myocardial infarction.

Severe right atrial hypertension may sometimes produce an abnormal PTF V<sub>1</sub>. In this situation the physical examination and the ECG usually reveal evidence of right atrial enlargement (Tall P waves > 2.5 mm.) and/or right ventricular hypertrophy. A P vectorcardiogram will show a clockwise loop in right atrial enlargement with abnormal PTF V<sub>1</sub> whereas in

left atrial enlargement the loop is counterclockwise. An echocardiogram will also be of value in the differential diagnosis of an abnormal PTF V<sub>1</sub> caused by left atrial enlargement as opposed to that due to right atrial enlargement. The ratio of the left atrial diameter to the root diameter is  $> 1.2$  in left atrial enlargement. In summary an abnormal PTF V<sub>1</sub> may be caused by (1) left atrial enlargement (2) acute left atrial hypertension without enlargement and (3) severe right atrial hypertension. The differential diagnosis of these conditions may be further elucidated by vectorcardiography and echocardiography. A more specific interpretation of the commonly used term "left atrial abnormality" may therefore be possible.

P A N Chandraratna MD MRCP  
Eugene Langevin DO  
Division of Cardiology  
University of Oklahoma  
Health Sciences Center  
P O Box 26901  
Oklahoma City Okla 73190

## REFERENCES

- 1 Morris J J Estes E H Jr Whalen R E Thorpe H K Jr and McIntosh H D P wave analysis in valvular heart disease. *Circulation* 29:190 1964
- 2 Chandraratna P A N and Hodges M. Electrocardiographic evidence of left atrial hypertension in acute myocardial infarction. *Circulation* 47:193 1973
- 3 Master A M P wave changes in acute coronary artery occlusion. *AM HEART J* 8:402 1933
- 4 Chandraratna P A N Nanda N C Shah P M Hodges M and Gramiak R. Echocardiographic study of the effects of acute left atrial hypertension on left atrial size. *J Clin Ultrasound* 4:15 1976
- 5 Braunwald E and Awe W C. The syndrome of severe mitral regurgitation with normal left atrial pressure. *Circulation* 27:29 1963
- 6 Zimmerman H A Bersano F and Dicoski C. The auricular electrocardiogram. Springfield Ill: Charles C Thomas Publisher 1968
- 7 Brown O R Harrison D C and Popp R L. An improved method for echocardiographic determination of left atrial enlargement. *Circulation* 50:59 1974

## Analgesic abuse and microvascular changes

The toxic effects of drugs on the kidney have been the subject of much research. In some instances the damage that occurs is clearly the result of hypersensitivity reactions but with many other drugs the exact mechanism responsible for the observed effects has not been elucidated. That analgesic abuse can cause renal papillary necrosis and cortical interstitial fibrosis has been well documented but the manner in which the renal papilla undergoes necrosis has largely eluded research workers. The recent observation of marked thickening occurring in the walls of small submucosal vessels of the renal tract in patients with analgesic nephropathy adds a new dimension to the possible pathogenesis of analgesic induced papillary necrosis. The microvascular changes described extend from the renal papilla to the submucosal vessels of the pelvis, ureter, and bladder. It is suggested that it is this thickening of the walls and resultant narrowing of the lumen in vessels of the renal papilla and pelvis that is responsible for the infarct like necrosis of the papilla that occurs in the presence of analgesic abuse. In those patients in whom the microvascular abnormality has been observed the excessive analgesic intake was either phenacetin or paracetamol containing compounds. Recent studies in patients with analgesic nephropathy have revealed that following the ingestion of phenacetin or paracetamol by these patients a greater than normal proportion of the drugs and their metabolites appear in the urine in a non conjugated form. It is not known whether this is an expression of a functional defect of hepatic microsomal enzymes or due to hormonal or bacterial deconjugating enzyme action within the urinary tract. Both are possible mechanisms and it is worth noting in this regard that patients with analgesic nephropathy have an excessive deposition of lipofuscin pigment in the liver and associated organelle damage as seen on ultrastructural examination. The non conjugated form of the excreted drug is more lipid soluble and tends to diffuse

back across the urinary epithelium through the submucosal tissue where it may have a deleterious effect upon the vascular tree. The vascular changes are seen to be most marked at those sites where one expects the drug to be present in high concentration namely the renal papilla and along the pathway of the urinary stream in the pelvis, ureter and bladder. In the latter site the changes are found mainly in the submucosal vessels where the ureter enters the bladder and to a much lesser extent in vessels away from this area. It is interesting to speculate as to whether the changes in the vessels are confined to the renal tract or whether the non conjugated drug which tends to persist in the body has similar toxic effects elsewhere in the organism. Preliminary observations suggest that some narrowing of dermal vessels may also occur in patients with analgesic nephropathy.

In summary we are of the opinion that the presence of these vascular changes in the renal tract and possibly the dermis in patients who abuse analgesics will open new vistas in the study of the toxic effects of drugs.

C Abrahams FRCPath FFPath(4)  
1609 Lister Building  
Jeppe Street  
Johannesburg  
A I Furman FRCP(Ed)  
D Salant FRCP(SA)  
Departments of Pharmacology  
and Medicine  
Medical School  
University of the Witwatersrand  
Johannesburg South Africa

## REFERENCES

- 1 Hesse V Van Tonder H and Abrahams C. Analgesic cystitis. *J Urol* 116:170, 1976

2. Abrahams, C., Van Tonder H., and Hesse V. Abnormal vessels in the urinary tract in man. *Arch Pathol Lab Med* 100:630 1958
3. Abrahams C. Cause of analgesic induced renal papillary necrosis. *Lancet* 2:346 1958
4. Furman H., I Galasko G F T and Block, C S. Decreased drug conjugation as a pathogenic factor in the

aetiology of analgesic nephropathy in Robinson B H B editor. *Dialysis transplantation nephrology Proceedings of EDTA* vol 13 1976 pages 443-450

5. Abrahams C, Wheatley A H, Rubenstein A H and Stables, D. Hepatocellular lipofuscin after excessive ingestion of analgesics. *Lancet* 2: 671 1964

## Of the mind of man

The greatest natural resource of any nation is the mind of man. The mind is most important in any endeavor of man regardless of its nature. And this is true in cardiology. The advancement in the field of cardiology from practically nothing of note in the dark ages of civilization to the developments and knowledge that exist today is remarkable. The greatest therapeutic advancement for the benefit of the sick was the discovery of penicillin. This antibiotic and many others which followed eliminated syphilitic heart disease and arterial aneurysms, eliminated death from bacterial endocarditis, made intricate cardiac surgery possible and helped to control and cure complicating and associated infections in cardiac diseases, etc. Better nutrition, public health, improved housing, clothing, and other changes reflect the fruits of the minds of people. By supporting thinkers, scholars, researchers, and teachers so that they can be free from the burdens and rules of accountability and the practices and pressures of popular research, teaching, and politics, man can tread into the future with confidence and continue the advancement of cardiology and medicine. Truth will prevail and false claims

succumb with time. Man with his active, fertile mind will assure the survival of man and the advancement of health and improvements in cardiology. *There is no need for example to fear critical shortage of energy. Let the mind of man be free and be encouraged to venture in thought and research and the energy shortage will be solved and all people will profit.* Cardiology has a great future through the mind of man. To cardiologists 100 years hence, the cardiology of today will appear archaic. This is to be expected because of the mind of man, the greatest resource of any nation. Nurture it, support it, unburden it, and keep it free.

G E Burch M.D.  
Tulane University School of Medicine  
and Charity Hospital of Louisiana  
New Orleans, La.

## REFERENCE

1. Burch, G E. Of scientific thought. *Arch. Intern. Med.* 102:855 1958



## Differences in Coronary Care Units

To the Editor

In a recent annotation (AM HEART J 91 673 1976) Lindholm and colleagues<sup>1</sup> challenged the value and effectiveness of coronary care. While their views certainly are shared by some, they would be rejected by the majority of cardiologists in this country. Perhaps the differences in attitude relate to what one calls a Coronary Care Unit. Australian coronary care units have followed the general pattern of the original unit established by Julian<sup>2</sup> at Sydney Hospital with patients having suspected or proven infarction being monitored in as peaceful an atmosphere as possible by nursing staff trained in intensive coronary care. The coronary care unit in Dr Lindholm's hospital as described elsewhere comprises beds with ECG monitoring facilities in a busy general medical emergency admission department.

In this country the hospital mortality rate for patients with definite infarction who progress through coronary care wards of major hospitals is around 16 per cent, and we hopefully look to further reduction of this figure with implementation of measures to reduce infarct size. If our hospital mortality figures were as high as those published by Dr Lindholm and colleagues—41 per cent for all patients, 33 per cent for those 69 and under—we would probably share his views. The published figures however suggest that Dr Lindholm and colleagues should look within their hospital for an answer before projecting their views to other hospitals with completely different arrangements (and results).

Michael O'Rourke M.D. FRACP  
Medical Professional Unit  
University of New South Wales  
St Vincent's Hospital  
Darlinghurst NSW 2010  
Australia

## REFERENCES

- 1 Lindholm J, Fabricius Bjerre N, Astvad K and Kjærulff J. Coronary care units. AM HEART J 91 673 1976.
- 2 Julian D G. Treatment of cardiac arrest in acute myocardial infarction. Lancet 2 840 1961.
- 3 Astvad K, Fabricius Bjerre N, Kjærulff J and Lindholm J. Mortality from acute myocardial infarction before and after establishment of a coronary care unit. Br Med J 1 567 1974.
- 4 McLean K H, Penington C and Sloman J G. The Australian coronary care unit. Review 1970. Med J Aust 1 753 1973.
- 5 O'Rourke M F, Fletcher M, Walsh B and Crowley A. Impact of the new generation coronary care unit. Aust N Z J Med 11 183 1976.

## Differential refractoriness of ventricular specialized conduction system

To the Editor

We have read with great interest the paper by Cannon Goldreyer and Damato entitled 'A demonstration of differential refractoriness within a single fascicle of the human

ventricular specialized conduction system' which appeared in the June 1975 issue of the Journal (AM HEART J 90 1975). The authors are the first to demonstrate with clinical electrophysiological methods that two areas of differential refractoriness may exist within the right bundle branch (RBB) of which the more distally located area is more refractory. They are the first to show an A-V gap phenomenon due to decreased conduction velocity in a proximal region of the RBB. We would like to make a comment concerning the maximal refractoriness within the RBB. The authors suggest that the effective refractory period (ERP) located relatively distal within the RBB represents the area of maximal refractoriness. Every premature supraventricular impulse which blocks below the His bundle does so at a site or area of maximal refractoriness. A zone of maximal refractoriness was initially encountered within the RBB when the premature impulse first blocked below the His bundle. We are not in agreement with this opinion.

Due to the limits of the indirect methods of clinical electrophysiology in the intact human heart, regions with longer ERPs in an electrophysiologically heterogeneous RBB can not be demonstrated if functional refractory periods (FRPs) of more proximal regions exceed the ERPs of the adjacent distal portions. Thus it is obvious that in the case demonstrated by the authors it can't be proved that the relatively distally located region with the longer ERP represents the region of maximal refractoriness. Within an even more distal area of a depressed RBB regions with longer ERPs may exist. Obviously the initial refractoriness can represent the maximal refractoriness but this possibility can be verified by the indirect techniques recently employed in clinical electrophysiology. We think that the title of the excellent paper reflects exactly our opinion concerning refractoriness: the authors demonstrate differential refractoriness within a single fascicle of the human ventricular specialized conduction system, and nothing more.

J. Tenczer M.D.  
L. Littmann M.D.  
3rd Department of Medicine  
Semmelweis University of Medicine  
1430 Budapest Hungary

## REFERENCE

- 1 Cannon D S, Goldreyer B N and Damato A A. Demonstration of differential refractoriness within a single fascicle of the human ventricular specialized conduction system. AM HEART J 90 1975.

## Arterial thromboembolic complications with aortic ball valve prostheses

To the Editor

In a review paper on arterial thromboembolic complications in patients with a Starr Edwards aortic ball valve prosthesis, Dale<sup>1</sup> concludes that arterial thromboembolic complications represent a major threat to patients even several years after the operation in spite of intense anticoagulant therapy. The

February 1978 Vol. 50 No.

conclusion implies a major shortcoming of such therapy. Fortunately however the author defines his aim and achievement with respect to the intensity of oral anticoagulation. The aim was 5 to 15 per cent Thrombotest only slightly more than one third of the patient values were  $\leq 10$  per cent in terms of Thrombotest.

The reader unfamiliar with oral anticoagulation controlled by Thrombotest is likely to accept the author's opinion that anticoagulation intensity in this range is adequate particularly because such Thrombotest values have long been and are still propagated as therapeutically optimal values in arterial thrombosis. On the Continent the Scandinavian protagonist of Thrombotest proposed at the introduction of Thrombotest in 1959 an optimal therapeutic range of 10 to 30 per cent. However this range has been applied without success in patients with the cloth-covered Starr Edwards prosthesis No 2300 aortic and No 6300 mitral. In spite of this failure a target value of  $15 \pm 5$  per cent is still haunting the literature in 1981. That anticoagulation with a high proportion of the Thrombotest values lying  $\leq 10$  per cent is unlikely to be successful can further be concluded from the results of many well designed clinical trials.\*

In The Netherlands where Thrombotest has been used since 1967 by an increasing number of laboratories responsible for laboratory control of outpatient oral anticoagulant treatment (at present more than 50 000 patients including a large number with a heart valve prosthesis) the therapeutically optimal range is 5 to 10 per cent with a target value range of 7 to 8 per cent. In three double blind trials on long term anticoagulation treatment performed in The Netherlands between 1965 and 1968 the values of 5 to 80 per cent of the patients lay below  $\leq 10$  per cent Thrombotest. At present with computer assisted regulation of the dosage of the anticoagulant, outpatients can easily be maintained at a level of  $\leq 10$  per cent for 80 to 85 per cent of the time.

Patients with a heart valve prosthesis should receive particularly tight and even more intensive treatment: the optimal range in terms of Thrombotest being 4.5 to 8 per cent with a target value range of 6 to 7 per cent. With this regimen we very seldom see thromboembolic complications in artificial heart valve patients, which is consistent with the results obtained in the well controlled study of a Canadian author.

It should be realized in this context that it is not only Dutch experience which has shown that Thrombotest takes an exceptional position. American and British experts in the field came to similar conclusions as early as 1967. That the Dutch intensity of treatment is not exaggerated is also evidenced by the risk of bleeding complications, which proves to be acceptable. It is clear however that the intensity of treatment as applied in The Netherlands is not exceptional as such, but only with respect to the terms of percentage coagulation activity according to the producers' standard reference curve. In those terms it is much lower indeed than in terms of the conventional percentages according to Quick maintained with any of the other thromboplastins used for anticoagulant control.

It is to be hoped that the report of the international prothrombin time standardization trial performed under the joint auspices of the International Committee on Standardization in Haematology (ICSH) and the International Committee on Thrombosis and Haemostasis (ICTH) will be used as a guide in national anticoagulant control panels for standardization of the prothrombin time and by this to a better

definition of the proper therapeutic range to be aimed at with the many different types of thromboplastin and methods of control. Once this has been achieved disappointing observations such as those reported by Dale should no longer occur.

M J Boekhout Mussert  
E Briet  
P van Brummelen  
H H P J Lemkes  
E A Loeliger  
Academisch Ziekenhuis  
Leiden  
The Netherlands

# REFERENCES

- 1 Dale J Arterial thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses. *AM HEART J* 91 553 1976
- 2 Nyegaard Thrombotest leaflet 1974
- 3 Owen P A Thrombotest A new method for controlling anticoagulant therapy. *Lancet* 2 754 1959
- 4 Cleland J and Molloy P J Thromboembolic complications of the cloth-covered Starr Edwards prostheses no. 3300 aortic and no. 6300 mitral. *Thorax* 28 41 1973
- 5 Tullis J L Clot Springfield Illinois 1976 Charles C Thomas Publisher
- 6 Friedli H, Arschide N, Grondin P, and Campeau L Thromboembolic complications of heart valve prostheses. *AM HEART J* 81 102 1971
- 7 Bergqvist D and Dahlgren S Leg vein thrombosis diagnosed by fibrinogen test in patients with fracture of the hip: a study of the effect of early prophylaxis with dicumarol or dextran. *Acta Med Scand* 192 121 1973
- 8 Bronge A, Dahlgren S and Lindquist B Prophylaxis against thrombosis in femoral neck fractures—a comparison between dextran and dicumarol. *Acta Chir Scand* 137 29 1971
- 9 Coon W W, Willis P W, and Symons M J Assessment of anticoagulant treatment of venous thromboembolism. *Ann Surg* 170 559 1969
- 10 Kanis J A Heparin in the treatment of pulmonary thromboembolism. *Thromb Diath Haemorrh* 32 519 1974
- 11 Moschos C H, Wong P C Y, and Sise M Controlled study of the effective level of long term anticoagulation. *J A M A* 190 799 1964
- 12 Pinto D J Controlled trial of an anticoagulant (warfarin sodium) in the prevention of venous thrombosis following hip surgery. *Br J Surg* 57 349 1970
- 13 Hamman J J, Hansen A, and Loeliger E A The value of long term coumarin treatment in peripheral sclerosis (clinical trial). *Thromb Diath. Haemorrh.* 21 405 1965
- 14 Meuwissen O J A Th, Vervorm M C, Cohen O, Jordan F L J, and Nelemans F A A double blind trial on long term anticoagulant treatment after myocardial infarction. *Acta Med Scand* 186 361 1969
- 15 Loeliger E A, Hensen A, Kroes F, Dijk L M, van Felken N, Jonge H de, and Hemker H C A double blind trial of long term anticoagulant treatment after myocardial infarction. *Acta Med Scand* 182 49 1967
- 16 Miale J B Laboratory control of anticoagulant therapy. *J A M A* 180 136 1962
- 17 Poller L Methods for the laboratory control of short term anticoagulant therapy. *Acta Haematol.* 28 168 1962

# Reply

## To the Editor

Dr Loeliger and associates criticize the intensity of the anticoagulant treatment reported in my paper<sup>1</sup> where the therapeutic range was considered to be from 5 to 15 per cent of normal coagulation activity as measured by Thrombotest (TT).<sup>2</sup> I agree that the therapy is optimal when the TT is kept between 5 and 10 per cent and this level is now propagated by the producer and is the accepted one in our country.

The slightly higher values had however been allowed mainly for two reasons. Firstly because the hazard of strict anticoagulation in such patients is severe bleeding and fatal intracranial or other types of hemorrhage are not rare.<sup>3</sup> Two patients in my study died from bleeding that occurred on TT values of 5 and 11 per cent. Patients with prosthetic ball valves might be particularly susceptible to hemorrhage because they have a considerably reduced platelet adhesiveness and a prolonged bleeding time. The recommendation by Dr Loeliger and associates that valve patients should have particularly intensive anticoagulation could therefore have serious consequences and I fear that an increased number of bleeding episodes would more than counterbalance a possibly better effect on thrombus formation.

Secondly slightly higher values were used because of the practical difficulties connected with control of anticoagulant therapy in patients living in all parts of Norway, often very far from the control laboratories. Nevertheless the intensity of anticoagulation was consistently satisfactory in approximately half of the patients even after the standards outlined by Dr Loeliger and associates and higher levels are accepted by several centers. Furthermore I have later collected information of all TT values throughout the period since the distribution of the values reported in the paper reflected only the levels at follow up. This demonstrated that 86 per cent of the values fell between 5 and 15 and 55 per cent fell between 5 and 10 per cent of normal activity. To my knowledge a more consistently intensive anticoagulant therapy in materials concerning patients with prosthetic valves has not been presented.

The relation between the intensity of the therapy and the incidence of arterial thromboembolic complications has been evaluated further. The rate of thromboembolism was however not lower in the patients with the majority of their TT values at 10 per cent or lower than in the others. This supports my conclusion that such complications represent a major threat to the patients in spite of intensive anticoagulant treatment.

Dr Loeliger and associates seek support for their assertion that intensive anticoagulation can effectively prevent arterial thromboembolism in patients with prosthetic heart valves from a Canadian study. This is surprising since they stress the importance of prothrombin time standardization because in that paper not even the type of thromboplastin used is mentioned. A direct comparison is therefore not possible but it is not improbable that the majority of my patients received what was considered satisfactory anticoagulation in that study. Furthermore only 33 patients received what was defined as adequate therapy and one had a thromboembolic complication. Moreover most patients had mitral or tricuspid valve replacement which would predispose for thrombi of a more venous composition. That this type of thrombus can be effectively prevented by anticoagulants is well established.

It is astonishing that Dr Loeliger and associates do not assert on this study alone since only 17 of the patients with single aortic valves had received adequate anticoagulation.

Dr Loeliger and associates state that they very seldom see thromboembolic complications in patients with artificial heart valves. A better documentation of the intensity of the treatment, its antithrombotic effect and the rate of bleeding complications would however be more valid.

Finally their assumption does not take into consideration the role of the platelets for the thrombotic process. While the dominant mechanism for venous thrombosis is plasma coagulation, platelet aggregation is important for the formation of arterial thrombi. Although adequate anticoagulation certainly is of some benefit it does not affect the reactivity of the platelets. Therefore arterial thrombosis on prosthetic aortic valves will most probably represent a problem even if very intensive anticoagulant therapy is given.

Jon Dals  
Institute for Thrombous Research  
Rikshospitalet Oslo  
Norway

## REFERENCES

- 1 Dale J. Arterial thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses. *AM HEART J* 91: 653 1976.
- 2 Owen P A. Thrombotest. A new method for controlling anticoagulant therapy. *Lancet* 2: 104 1969.
- 3 Cleland J and Molloy P J. Thromboembolic complications of the cloth covered Starr Edwards prostheses: no 2300 aortic and no 6300 mitral. *Thorax* 28: 41 1973.
- 4 Fredrik B, Aernichde N, Grondin P and Campe L. Thromboembolic complications of heart valve prostheses. *AM HEART J* 81: 702 1971.
- 5 Duvoisin G E, Wallace R B, Ellis F H, Andersen M W and McGoon D C. Late re-evaluations of cardiac valve replacement. *Circulation* 37 and 38 (Suppl. III): 3 1968.
- 6 Albanian M, Austen W G, Yurchak P M and Scannell J G. Thromboembolic complications of prosthetic cardiac valves. *Circulation* 37: 876 1968.
- 7 Matloff J M, Collins J J, Sullivan J M, Gotlin R and Harken D E. Control of thromboembolism from prosthetic heart valves. *Ann Thorac Surg* 8: 133 1979.
- 8 Reed G B, Clausen R H, Tice D A and Akinspur A J. Five year experience with Magovern aortic prostheses. *Circulation* 43 and 44 (Suppl. I): 73 1971.
- 9 Bjørk V O, Henze A and Holmgren A. Five year experience with the Bjørk Shiley tilting disc valve in isolated aortic valvular disease. *J Cardiovasc Surg* 16: 451 1975.
- 10 Dale J and Myhre E. Platelet functions in patients with aortic ball valves. *AM HEART J* 94: 339 1977.
- 11 Lam Po-Tang P R L C and Potter L B. Oral anticoagulant therapy and its control. An international survey. *Thromb Diath Haemorrh* 34: 419 1975.

## More on high school health curricula

### To the Editor

I was relieved to discover that the problem of an inadequate and inappropriate high school health curricula was at last cited by Dr Wroczek in the *AMERICAN HEART JOURNAL*. I would like to add three points to his editorial.

My first point is to label high school health textbook material as also being inadequate and inappropriate. If you will observe the contents of most high school (and some college) health texts you will discover an imbalance in subject matter favoring subjects other than cardiovascular disease and cancer. The one thing that I can remember from my high school health education is the proper procedure for brushing my teeth. Cardiovascular disease was not even mentioned in high school curriculum at this time (early 1960s). I believe high school health care texts should be jointly authored by the physician, exercise physiologist, and health educator alike.

My second point is more specific to my own profession. High school physical education classes are often an unstructured and non-educational experience. Inappropriate curricula is the culprit here as well. Overemphasis on superior athletic performance, body physique, and non-dynamic forms of exercise have been the rule rather than the exception. Cardiovascular endurance types of exercises and recreation should be at least 60 per cent of the emphasis. If secondary school curriculum specialists would just wake up and start reading even a portion of current medical literature relating to exercise physiology, the problem would be partially solved.

Finally, my last point is what I believe to be the crux of the problem. The training of health educators at the college level is far out of line. Speaking from my own experiences, some of the nation's largest and supposedly most prestigious universities are the most misaligned with regard to the training of secondary school health educators. Regardless of how well we improve college level health education textbooks, we still see the type of professor who remains bolted to a few 40-year-old ideas. I am speaking specifically about neglecting to teach lifelong cardiovascular endurance exercise habits and how they frequently have a positive effect on CHD related risk factors. Nearly every significant piece of research that has been published in the last 6 years has been either ignored or is contrary to what is presently taught in many high school physical education classes. There is no excuse for ignorance regarding the proper forms of exercise when you consider the availability of current publications.

My suggestion is that we re-educate some of the professors who are responsible for instilling (or not instilling) health care information into our secondary health education teachers. One step further—evaluate the chairmen of university health, physical education, and recreation departments.

Ralph L. LaForge, M.Sc.  
Physiologist  
Lovelace Bataan Medical Center  
Preventive Medicine  
5400 Gibson Blvd. SE  
Albuquerque, N.M. 87108

## REFERENCES

1. Committee on Exercise American Heart Association. Exercise testing and training of apparently healthy individuals. New York 1977. American Heart Association, pp. 1-6, 40.
2. American College of Sports Medicine. Guidelines for graded exercise testing and exercise prescriptions. Philadelphia 1975. Lea & Febiger Publishers, pp. 23-49.
3. Folkick M. The quantification of endurance training programs. In: Exercise and sports sciences reviews, vol. 1. Wilmore J. ed. New York 1973. Academic Press, Inc. pp. 15-18.

4. Fox S.M., Naughton J.P. and Gorman P.A. Physical activity and cardiovascular health: the exercise prescription. Mod. Concepts Cardiovasc. Dis. 41:6 1972.
5. Astrand, P.O. and Rodahl, K. Textbook of work physiology. New York, 1977. McGraw-Hill Book Company, Inc. chapters 12, 16 and 17.
6. Matthews D.K. and Fox M.L. The physiological basis of physical education and athletics. 2nd ed. Philadelphia 1911. W.B. Saunders Company, section 4 and chapter 21.
7. Cooper H.H. et al. Physical fitness levels vs. selected coronary risk factors. J.A.M.A. 235:168 1976.
8. Mroczek W.J. High school health curricula: A neglected medical resource. AM. HEART J. 92:21 1976.

## Nitroglycerin ointment therapy and leg edema

### To the Editor

Topically applied nitroglycerin ointment has been well demonstrated to have a sustained vasodilatory effect and therefore its use has become fairly commonplace in the chronic therapy of angina pectoris and congestive heart failure.

It has also been demonstrated that the major vasodilatory action of nitroglycerin is on the venous circulation, resulting in a reduction in venous return and left ventricular filling pressure (preload).

I have recently observed two cases in which the onset of gross lower extremity edema followed within one week the institution of nitroglycerin ointment therapy.

The first case is that of a 67-year-old man who because of chronic severe angina was placed on 2 per cent nitroglycerin ointment 1 inch application every 4 hours one week prior to admission for coronary angiography. Beginning about five days prior to admission this man who had never had any previous symptoms of congestive heart failure began to note the onset of pedal edema for the first time. By the time of admission his house physicians noted new 3+ edema of his right leg, the source of a saphenous vein for earlier coronary artery bypass grafting and 1 2+ edema of his left leg and initially felt that he had developed congestive failure. Closer examination, however, revealed no other evidence of right or left heart failure. The edema resolved easily with diuretic therapy. Later therapy with nitroglycerin ointment 1 inch application every 4 hours plus hydrochlorothiazide 50 mg by mouth every day resulted in no further edema.

The second case is that of a 66-year-old man with chronic biventricular failure secondary to diffuse coronary disease with diffuse left ventricular hypokinesis, mitral regurgitation and an elevated left ventricular end-diastolic pressure of 70 demonstrated by catheterization in 1973. Since that catheterization he has had several admissions for control of his congestive heart failure, the last being in February 1977 at which time measurements via a balloon tipped thermostator catheter revealed a cardiac index (CI) of 1.4 and pressures as follows: right ventricle 60/23, pulmonary artery 60/34 and mean pulmonary capillary wedge (PCW) 33 mm Hg. He was initially treated with small doses of intravenous nitroglyceride (0.05 µg/Kg/hr) which resulted within 24 hours in a marked improvement in dyspnea associated with an improvement in his CI to 2.3 and PCW to 16. He was then switched to non-parenteral therapy and was eventually discharged on digoxin 0.125 mg twice a day, hydralazine 30 mg four

times a day KCl 20 mEq twice a day and 2 per cent nitroglycerin ointment 1 inch every 6 hours

One week after discharge he presented with a 5.8 kilogram weight gain over his lowest hospital weight and painful 4+ peripheral edema though experiencing continued relief of dyspnea his previous limiting symptom and continued roentgenographic clearing of the lung fields. Despite discontinuation of his nitroglycerin therapy elevation of his legs and more diuretic therapy his edema has been very difficult to resolve.

The temporal relationship of the onset of peripheral edema (or sudden worsening thereof) in these two patients to the institution of nitroglycerin ointment therapy suggests a link between the two. The likely sequence of events in the genesis of the edema is that nitroglycerin ointment causes sustained venodilatation which leads to venous pooling which eventually results in high peripheral venous hydrostatic pressure which of course results in transudation of fluid. In the first case this sequence was probably aided by previous stripping of the right superficial saphenous vein. In the second case the sequence was probably aided by persistent poor pump function and also perhaps by hydralazine therapy which by lowering arterial resistance would allow ready forward access of fluid to the capacitance vessels.

These two cases represent good clinical demonstrations that nitroglycerin ointment does have a sustained hemodynamic effect and that its venodilatory effect is a strong one. The onset of new or worsening peripheral edema soon after the institution of nitroglycerin ointment therapy should be watched for and recognized as a possible side effect of that therapy especially in patients with predisposing conditions such as poor left ventricular pump function and pre-existing venous insufficiency.

St George T Lee Jr M.D.  
University of Virginia Hospital  
Charlottesville Va 22901

# REFERENCES

- 1 Meister S G Furr C Festosa G Bostrom K Frankl W and Engel T R Sustained hemodynamic effect of nitroglycerin ointment (Abstr) *Am J Cardiol* 37 155 1976
- 2 Mikulic E Franciosa J A and Cohn J N Comparative hemodynamic effects of nitroglycerin forms in heart failure (Abstr) *Circulation* 52(Suppl 11) 11 36 1975
- 3 Taylor W R Forrester J S Magnusson P Takano T Chatterjee K and Swan H J C The hemodynamic effects of nitroglycerin ointment in congestive heart failure (Abstr) *Circulation* 52(Suppl 11) 11 36 1975
- 4 Chatterjee K and Parmley W W The role of vasodilator therapy in heart failure *Progr Cardiovasc Dis* 19 301 1977
- 5 Mason D T and Braunwald E The effects of nitroglycerin and amyl nitrate on arterial and venous tone in the human forearm *Circulation* 32 755 1965
- 6 Flaherty J T Reid P R Kelly D T Taylor D R Weissfeldt M L and Pitt B Intravenous nitroglycerin in acute myocardial infarction *Circulation* 51 132 1975
- 7 Armstrong P W Walker D C Burton J R and Parker J O Vasodilator therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin *Circulation* 52 1118 1975

# References—dog s tails?

## To the Editor

Who would submit a medical article for publication without a comprehensive appendage of references doing back as possible to Gutenberg? At present authors seem to think the references adorn an article and the greater their number the more they bespeak the diligence of the author, their knowledge of the literature their erudition and the accessibility of a well stocked library. The number of references in the average article makes one think that the tail is wagging the dog.

This is a plea not only to save paper and ink and the tired editors and reviewers but to limit references to those most recent articles on a subject indicating that all that has been written in the past will be found in them. For example

## REFERENCES

1 26 of 27

27 Taylor E F Dogs tails *Am J Canis* 88 19, 1977

Richard J Kennedy M.D.  
Chief Electrocardiograph  
Vectorcardiography and Echocardiography  
Dept of Medicine  
St Vincent's Hospital and Medical Center  
of New York  
153 West 11th St  
New York N Y 10011

# Chromosome aberration in ectopia cordis (46 XX 17q+)

## To the Editor

Thoracic ectopia cordis is a rare congenital malformation which usually results in death soon after birth. Although many reports exist on management of patients with various types of ectopia cordis very little information is available regarding its etiology. Specifically the paucity of data on chromosome studies in these patients is striking. Following is a brief description of a patient with ectopia cordis in which chromosome studies showed additional chromosome material attached to the long arm of chromosome 17.

## Case report

Patient B H a 2550 gram Caucasian female infant was born at 36 weeks gestational age. Multiple congenital anomalies including thoracic ectopia cordis cleft lip and palate and hydrocephalus were noted at birth. The infant died at 7 hours of age. Additional autopsy findings were tetralogy of Fallot with extreme dextroposition of the aorta anomalous origin of the left coronary artery bilobed right lung and occipital meningocele. The pregnancy was complicated by a septic uterus and pre-eclampsia. Medications ingested during the first 3 months of pregnancy included Combid sparsule capsules and Bendectin tablets. Fetal bradycardia of 40/minute was noted during labor. The mother was a 21 year-old primigravida. The father was 26 years old. Both parents were in good health and their respective family histories were negative for birth defects. Consanguinity was denied. Chromosome analysis using peripheral blood from the infant showed

extra material on chromosome 17 (46,XX 17q+) The origin of this material could not be established Cytogenetic studies of the parents showed no abnormalities.

The discovery of a chromosome abnormality in this patient with ectopia cordis is to the best of our knowledge the first reported such case It may be that this is an entirely coincidental finding since a patient with thoracic-abdominal ectopia cordis and normal chromosomes has been reported Nevertheless, it appears that further cytogenetic studies on these patients utilizing advanced techniques are necessary before the possibility of a chromosome aberration can be eliminated The drugs ingested by the mother during pregnancy may also be considered teratogenic but we are not aware of any report indicating such a relationship at present

Burhan Say M.D.  
Carla E Wilsey M.D.  
Department of Pediatrics  
Children's Medical Center  
University of Oklahoma  
Tulsa Medical College  
Tulsa Okla 74135

#### REFERENCE

- 1 Toyama W M Combined congenital defects of the anterior abdominal wall sternum diaphragm pericardium and heart A case report and review of the syndrome Pediatrics 50 7 8 1975

#### Excitation-contraction abnormalities and heart block

To the Editor

We have read with great interest Dr Burch's short article on the time course of contraction of the myocardium and its effect upon myocardial function in a recent issue of the JOURNAL.

It is reasonable to suppose that excitation-contraction relationships in the heart are very important and that abnormalities in the time course of contraction may be responsible for intraventricular bundle branch block Dr Burch mentions RBBB LBBB and arborization block or defective intraventricular conduction but fails to discuss the WPW blocks (LV RV septal types) and the pre-excitation syndrome These are very real problems in cardiology

Is it not reasonable to suppose that some contraction abnormalities, even more complicated than those that occur in RBBB LBBB and arborization block are responsible for Wolff-Parkinson-White blocks in patients? This point is certainly a very important one

Dr Burch is doubtless aware of the work of Lenègre on the bundle branch blocks the latter's investigations have indicated that most cases of intraventricular block have intraventricular cavity dilatations Is it not possible to presume that excitation-contraction abnormalities in patients with defective intraventricular conduction systems may be one of the causes of ventricular dilatation and failure in the Wolff-Parkinson-White syndrome as well as in the others

Dr Burch's article gives us an excellent explanation of different disturbances in the order of electrical activation of

the myocardium on conduction system defects but we would like to see if possible a more detailed study on each separate manifestation of bundle branch blocks.

Asim Istanbullu M.D.  
London England  
Suha Veldet M.D.  
Postgraduate Teaching Hospital  
Haydarpaşa Numune  
Istanbul Turkey

#### REFERENCE

- 1 Burch G E Of the conduction system and myocardial function AM HEART J 92 809 1976

#### Aortic valve prostheses rheumatic fever and lone aortic regurgitation

To the Editor

I have recently commented on the late development of mitral stenosis in patients who have had mild to moderate mitral regurgitation following their initial attack of acute rheumatic fever An interesting observation in patients who have undergone aortic valve replacement eight to twelve years ago for apparent isolated aortic regurgitation deserves comment. These patients were young patients and were known to have had rheumatic fever With continued follow up it has become apparent that some will develop mitral valve disease years later<sup>1</sup> Quite obviously although aortic valve replacement changes the natural history of that valve it does not change the pattern of mitral valve disease In the last six months two patients have been found to have developed mitral stenosis and the insufficiency of mitral valve deformity In both patients this diagnosis was suspected by the appearance of a diastolic rumble and a fast opening snap The appearance of a new systolic murmur at the apex radiating to the axilla has clinically been a difficult auscultatory phenomenon to evaluate in patients with Starr-Edwards prostheses because of the wide radiation of the systolic flow murmur of this particular valve Careful repeated evaluations by the same observer may give a clue by the change in the character of the systolic murmur with passing years In both patients an echocardiogram supported the diagnosis of mitral valve disease and in one cardiac catheterization was also confirmatory Both patients presented with increasing cardiac symptomatology increasing shortness of breath, palpitation and fatigue

Two specific points must be made Firstly worsening of cardiac symptoms in a patient with an aortic valve prosthesis need not be related to prosthetic valve malfunction or myocardial disease but may obviously be related to the late development of mitral valve disease The clinical diagnosis of this may be partially obscured by the auscultatory findings associated with the prosthetic valve Echocardiograms are invaluable in further evaluation Secondly lone aortic regurgitation in young people is frequently rheumatic in origin As we have shown previously aortic regurgitation is the more persistent of the two lesions of acute rheumatic fever (aortic regurgitation and mitral regurgitation) It is the new appearance of lone aortic regurgitation in the older group that should raise the question of an etiology other than rheumatic fever

Lone aortic regurgitation in young patients may ultimately become combined aortic and mitral disease of the older patient with rheumatic heart disease

Howard H Kloth MD FACC FCCC

Member ICHD

Sub committee RHF & Rheumatic

Heart Disease

12 East 76th St

New York N Y 10021

# REFERENCES

- 1 Kloth H H Rheumatic and non rheumatic mitral valve disease *Circulation* 52 355 1975

- 2 Taranta A Fiedler J P Gilson III S Gordon L Hufnagel C A Kloth H H Markowitz M 1 Wannemaker L W Report of Intersociety Committee for Heart Disease Resources Community Resources for the Management of Patients with Rheumatic Heart Disease *Circulation* 44 A273 1971
- 3 Spanuolo M Kloth H H Taranta A Doyle E 1 Pasternack B The natural history of rheumatic aortic regurgitation: Clinical criteria predictive of death, congestive heart failure and angina in young patients *Circulation* 44 368 1971
- 4 Selzer A and Cohn K E Natural history of aortic stenosis: A review *Circulation* 45 8/8 1972

## Book reviews

**The Pathology and Surgery of the Veins of the Lower Limb** 2nd Ed. Edited by Harold Dodd and Frank H. Cockett. New York 1976 Churchill Livingstone 323 pages. Price \$39.50

The second edition of *The Pathology and Surgery of the Veins of the Lower Limb* edited by Dodd and Cockett is an excellent book on a common and too frequently mismanaged disease. There are six contributors to the book. The discussions of anatomy, pathology and physiology are clinically oriented to make it easier for the surgeon and other physicians to manage better venous diseases of the legs. The book consists of three parts. Part I is concerning with history, anatomy and physiology. Part II with pathology and surgery of the deep and communicating veins. The book is excellent and certainly a source of information essential for those who treat venous diseases of the legs, whether or not it is surgical or medical management. The illustrations are excellent. The reviewer is impressed with the poor application of a bandaging in general use. Figs 183 and 184 on pages 217 and 273 illustrate a smooth application but this usually remains smooth for a few minutes to a few hours and the patient finally finds his leg is encircled by multiple garters which impair venous return even more. Even stockings can cause difficulties especially those applied on the leg below the knee in which the upper edges are tight and act as garters. The various problems concerned with the use of stockings bandaging and full support is not emphasized sufficiently. The panty hose type custom fit are certainly worth serious consideration for venous support in the legs. This is a highly recommended book.

**Hypertension and Stroke Control in the Community** Edited by S. Hatano, I. Shigematsu and T. Strasser. Geneva 1976 World Health Organization 367 pages. Price \$17.00

This is the proceedings of a WHO meeting held in Tokyo during March 1974 on the control of hypertension and stroke. The papers and discussions are good. The statistical and epidemiologic data are interesting. The problems of management of mild hypertension and the community approach to the control of hypertension and stroke and their consequences are reviewed very well. The sections of the book concerning the discussions among the participants are most interesting. This publication summarizes very well the WHO programs and recommendations on hypertension and stroke based on a statistical and epidemiological point of view as well as the clinical.

**Quick Reference to Cardiovascular Diseases** Edited by Edward K. Chung. Philadelphia 1977 J. B. Lippincott Company 468 pages. Price \$20.00

This book edited by Chung is an interesting and useful presentation of clinical cardiology in a brief condensed manner. There are 36 contributors to this publication all capable cardologists. The diseases and problems discussed are the common ones encountered by clinicians daily. Each contribution is written concisely and in a summary type approach. The references cited are well chosen and again clinically oriented. This reviewer is of the opinion that the outline manner of describing the clinical problems will require a great deal of supplemental reading in order to

understand better the symptoms, signs, management, drug action and other phases of the illnesses. For those who are well informed the manner of presentation is extremely useful for a rapid review of the various common clinical problems. Diagnoses, pathophysiology and management are emphasized. This is a recommended and useful addition to the cardiology literature. The busy practicing physician will especially appreciate this publication.

**Microcirculation: Blood Vessel Interactions Systems in Special Tissues** volume I. Edited by John Grayson and Walter Zung. New York 1977 Plenum Press 470 pages. Price \$37.00

Volume I of *Microcirculation* edited by Grayson and Zung represents the proceedings of the First World Congress for the Microcirculation held in Toronto June 15 to 20 1976. As with other proceedings of symposia, this one contains the papers presented at the meetings. The 179 presentations are briefly and well summarized in one to two pages each. These brief presentations which are essentially abstracts make it possible for the reader to obtain the essential aspects of the studies. The reader can then follow up his interest by contacting the authors for further information or he can approach the literature directly and more extensively. The subjects discussed were quite numerous and include several presentations on blood and blood vessel interaction, methods, red cell interactions with the microcirculation, blood vessel structure, microcirculatory flow patterns, formed elements of the blood, platelets and thrombosis, lymphatics, pulmonary circulation, myocardial blood flow, splanchnic circulation, skeletal muscle and the microcirculation in other tissues. The papers are well written and present nicely the important aspects of the studies in a concise manner. This book certainly will be welcomed by busy readers. Those readers who are interested in details of technique and results will be forced to resort to further sources of information. This is a highly recommended publication on a much neglected important subject.

**Diagnosis and Management of Medical Emergencies** second edition. Edited by Rustom Jalilaki, M.D. and Farokh Erach. Udaewa, MD. New York 1977 Oxford University Press 50 pages. Price \$24.00

This second edition of *Diagnosis and Management of Medical Emergencies* should interest cardiologists since cardiac problems are frequently responsible for the medical emergencies encountered in medical practice. Emergency room physicians will find the book useful. The 11 chapters include among the many types of medical emergencies: cardiac, vascular, respiratory, shock, and industrial and accidental emergency states. The many contributors mainly from Bombay, India include diagnosis and differential diagnosis along with management. As the pace of living, industrial activity and aging of people increase, emergency treatment is becoming more and more important in the practice of medicine. This somewhat encyclopedic book is a useful publication that is entirely clinically oriented. This second edition continues to be an important publication in medicine and is recommended as a reliable practical book for cardiologists who are so often consulted to assist in the management of emergency disease states.



Lone aortic regurgitation in young patients may ultimately become combined aortic and mitral disease of the older patient with rheumatic heart disease

Howard H Kloth MD FACC FCCC

Member ICHD

Sub committee RHF & Rheumatic

Heart Disease

12 East 76th St

New York N Y 10021

# REFERENCES

- 1 Kloth H H Rheumatic and non rheumatic mitral valve disease Circulation 52 355 1975

- 2 Taranta A Friedler J P Gilson H S Gorda L Hufnagel C A Kloth H H Markowitz M Wannamaker L W Report of Intersociety Committee for Heart Disease Resources Community Resources for the Management of Patients with Rheumatic Heart Disease Circulation 44 A713 1971
- 3 Spanuolo M Kloth H H Taranta A Doyle E Pasternack B The natural history of rheumatic aortic regurgitation Clinical criteria predictive of death congestive heart failure and angina in young patients Circulation 44 368 1971
- 4 Selzer A and Cohn K E Natural history of aortic stenosis A review Circulation 45 818 1972

## Editorial

### International cardiology

J F Goodwin MD\*

London England

Cardiology developed at a rapid pace in the immediate years following the Second World War as a result of introduction of techniques of cardiac catheterization and angiocardiology and of the growth of cardiac surgery. These developments were aided by improvements in communication and by easier methods of travel which went towards meeting the increasing needs of scientists in all countries to exchange information. At the same time the developing countries were urgently in need of help with training programs, cardiological education and with identification of priorities in tackling these and allied problems.

The increasing incidence of cardiovascular disease especially coronary artery disease emphasized the necessity of collaboration among nations in developing programs of prevention and treatment and also the need for meetings to discuss and share the results of research. The continuing incidence of severe rheumatic heart disease in the developing countries imposed an important claim on available resources.

Even before the Second World War the need for international meetings was demonstrated by the gathering of a group of internationally known cardiologists in Prague in 1933. This was followed in 1944 by the Congress of the Inter American Society of Cardiology in Mexico City at the time of the foundation of the Institute of Cardiology. The Director Dr Ignacio Chavez invited a number of internationally famous cardiologists

including Drs Paul White, Samuel Levine, Carl Wiggers and Louis Katz from the USA. In 1946 the first International Council of Cardiology was formed and was charged with the task of laying the foundations of an International Society and with organizing the First World Congress of Cardiology to be held in 1950. Among the members of the Council were Sir John Parkinson of Great Britain, Professor Laubry of France, Professor Gustav Nelin of Sweden, Dr Paul White of Boston and other distinguished cardiologists.

The European Society of Cardiology was founded in 1947 on the occasion of the Third Inter American Congress of Cardiology in Chicago.

The First World Congress of Cardiology was held in Paris in 1950 under the Presidency of Professor Laubry. One thousand cardiologists attended and 486 scientific papers were presented. These were very small numbers by present standards but it was a noble beginning. The International Society of Cardiology (ISC) was formed at this time with the following statutes:

1 To stimulate the development of Cardiology in all its aspects: application, instruction, research, prevention of cardiovascular disease, help to cardiologists and help to cardiac patients.

2 To improve scientific exchange as well as technical and material cooperation between the affiliate societies of cardiology.

3 To contribute to the scientific development of its members and to the maintenance of ethical standards in the exercise of the specialty.

4 To organize and support courses, confer

From the Royal Postgraduate Medical School, London, England.  
Received for publication May 23, 1977.

Reprint requests: J F Goodwin MD, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS, England.

Presented to the International Society and Federation of Cardiology.

## Books received

**Long term Surgical Results in Children** Progress in Pediatric Surgery Vol 10 Edited by P P Rickham W Ch Hecker and J Prévot Baltimore 1977 Urban & Schwarzenberg 303 pages Price \$29.50

**Biofeedback & Self control 1976/77** An Aldine Annual on the Regulation of Bodily Processes and Consciousness Edited by Joe Kamiya T X Barber Neal E Miller David Shapiro and Johann Stoyva Chicago 1977 Aldine Publishing Company 597 pages

**Microvascular Reconstructive Surgery** By Bernard McC O'Brien BSc MS FRCS Churchill Livingstone New York 1977 350 pages Price \$38.00

**Pediatric Echocardiography** By Richard A Meyer MD with chapters by Russel L Uphoff BS and with the

assistance of Joan Korfhagen RDMS Philadelphia 1977 Lea & Febiger Publishers 203 pages Price \$11.00

**Infant and Child Care in Heart Surgery** By Robert M Goff MD Delos M Cosgrave MD and Aldo H Castañeda MD Chicago 1977 Year Book Medical Publishers, Inc 137 pages

**Trends in Computer processed Electrocardiograms** Edited by J H van Bommel and J L Willems Amsterdam, The Netherlands 1977 North Holland Publishing Co 430 pages Price \$46.95

**Sang et Toxiques** Collection de Médecine Légale et de Toxicologie Médicale 4<sup>es</sup> Journées du Groupement Français des Centres Anti Poisons Paris 1977 Editions Masson 220 pages

## Announcements

### Recent Advances in Cardiopulmonary Care IV

A seminar entitled Recent Advances in Cardiopulmonary Care IV sponsored by Memorial Hospital Sarasota Fla will be held on March 2 and 3 1978 at the Holiday Inn Lido Beach Sarasota Registration fees are \$50 for physicians and \$40 for nurses and others Twelve contact hours of continuing education units (CEUs) will be given

For further information regarding this seminar please contact Human Resources Development Department Memorial Hospital 1901 Arlington St Sarasota Fla 33579 Telephone (813) 959 1767

### Seventh Annual Cardiology Symposium

The Johns Hopkins Medical Institutions announces that the Seventh Annual Cardiology Symposium A Review of Changing Concepts Current Management and New Techniques and Therapies will be held June 1 through 3 1978 at the Cross Keys Inn Baltimore Maryland For further information contact Dr J O Neal Humphries Carnegie 568 The Johns Hopkins Hospital Baltimore Maryland 21205

### Geriatric seminar

A seminar entitled Geriatric Pow Wow will be conducted on April 7 through 9 1978 at the Arizona Inn 2200 E Elm St Tucson Ariz 85719 under the auspices of the University of Arizona College of Medicine Office of Continuing Medical Education This seminar is accredited by the Council on Medical Education of the American Medical Association for 16 Category I credit hours For further information please contact Office of Continuing Medical Education (Attn Katharine Bloch) University of Arizona College of Medicine Arizona Health Sciences Center Tucson Arizona 85724 Telephone (602) 682 6173

### The Lucien Dautrebande prize

The Fondation de Physiopathologie Professeur Lucien Dautrebande will award its next prize of about 3000 Belgian francs in 1979 The award will be presented for a work on human or animal clinical physiopathology preferably having therapeutic implications Applicants must submit their candidature before December 15 1978 to be considered for the award For further information regarding this competition please write Office of the Fondation de Physiopathologie Professeur Lucien Dautrebande 35 chaussée de Liège 590 Huy Belgium

### National Symposium on Aging

The University of California San Francisco Schools of Dentistry Medicine Nursing and Pharmacy and the Division of Continuing Education Health Sciences present a two-day symposium entitled The National Symposium on Aging to be held on February 25 and 26 1978 in San Francisco For further information please contact Program Chairman National Symposium on Aging Division of Continuing Education Health Sciences Univ of Cal San Francisco Cal 94143

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published Authors will be consulted when possible regarding republication of their material

Foundations explaining the reasons for the merger and asking them to approve it. All the replies that were received were in favor. Simultaneously the International Cardiology Federation circulated all its National Foundation members and received similar replies.

The merger was thus confirmed at the Long Range Planning Committee meeting in November 1976.

The Assembly of the ICF agreed to dissolve at its meeting in January 1977 on the understanding that the Assembly of the ISC would do likewise in Tokyo in 1978 at the Eighth World Congress of Cardiology. Because of the difference in timing of the Assemblies of the two organizations the ISFC could not be finally ratified on a permanent basis for a further 20 months. It would thus for practical purposes work entirely as a single society in order to promote its objectives and in particular to encourage and maintain the work of the Scientific Councils and the lay education programs. The ISFC was notified as a new society under Swiss Law in Geneva in early January 1977 and the first meeting of the Joint Executive Board was held in London in February 1977. The names of the Executive board are as follows:

- President Professor John Goodwin MD  
Great Britain  
1st Vice President Dr N J C M Kappeyne  
van de Copello The Netherlands  
Immediate Past President Dr Lysle  
Peterson MD USA  
Past 1st Vice President Dr L E  
January MD USA  
Administrative Secretary Mr K Meister  
Denmark  
Medical Secretary Dr Pierre Moret MD  
Switzerland  
Treasurer Mr E MacDonald Canada  
Chairman of the Scientific Board  
Professor Franz Gross MD W Germany  
Chairman of the Public Education  
Committee Mr Finn Monahan Lure  
President of the Asian Pacific Society of  
Cardiology Dr Morton Berk MD USA  
President of the European Society  
of Cardiology Dr H Denolin MD Belgium  
President of the Inter American Society of  
Cardiology Dr E Hirschaut MD Venezuela  
Chairman of the Financial Support Committee  
To be appointed

It is a pleasure to acknowledge the important work of Dr Lysle Peterson when President of the ISC and of Mr Kappeyne when President of the ICF in promoting the merger. Without their tireless work and patience the merger might never have been achieved so that international cardiology is much in their debt.

The immediate aims of the ISFC are to raise sufficient funds to maintain its programs and the administration necessary to direct and support them and to sponsor and assist in every way possible the activities of the Scientific Councils and the Public Education Committee. Clearly these activities cannot be sustained without adequate funds. Financial support must be raised by subscription from the national Societies and Foundations which are members of the ISFC. In return the ISFC will perform important functions in the realms of scientific communication, lay education and sponsorship of meetings. Funds are necessary to support the Scientific Councils in their functions of research and teaching and also the Public Education Committee. A good example of the work of the latter is the World Hypertension Year 1978 which is an exercise in public education supported by WHO. The Scientific Councils are intensely active and organize their own workshops and teaching programs. Where appropriate multicenter collaborative research programs are mounted such as that on Congestive Cardiomyopathy organized by the Council on Cardiomyopathy.

The formation of the Scientific Councils of the International Society of Cardiology from the original research committee was an important and significant event which took place at the Fifth World Congress of Cardiology in New Delhi in 1966. At the present time seven Scientific Councils make up the Scientific Board which is under the Chairmanship of Professor Gross of Heidelberg. The Councils are as follows:

1. Arteriosclerosis and Ischaemic Heart Disease  
Chairman Dr G Schettler (West Germany)
2. Council on Cardiomyopathies  
Chairman Dr E Olsen (Great Britain)
3. Council on Epidemiology and Prevention  
Chairman Dr J Stamler (USA)
4. Council on Hypertension  
Chairman Dr J I S Robertson (Great Britain)
5. Council on Paediatric Cardiology  
Chairman Dr K Bossna (The Netherlands)
6. Council on Rehabilitation of Cardiac Pa

ences, publications and other activities deemed necessary for the realization of the aims noted above

5 With the same objectives, to sponsor World Congresses of Cardiology every four years

These statutes have not changed substantially in the last 25 years

Since 1950 World Congresses of Cardiology (as everyone knows) have been held every four years, the Eighth being due in Tokyo in 1978. The European Society of Cardiology has held its congresses also every four years two years between each World Congress. The Inter American Society also holds Congresses in the same year as the European Society. The Asian Pacific Society of Cardiology, which was formed in 1956 at the suggestion of Dr White holds its Congresses in the same year as the European and Inter-American Societies.

Thus there were in 1976 three continental societies and one world society in addition to many national societies affiliated to the International and appropriate regional Continental Societies. In addition the American Heart Association provides the United States of America and the World with a vital, active, and thriving combined Cardiac Society and Foundation. The inauguration of the American College of Cardiology in 1975 provided a further stimulus for education, teaching and research on both national and supra national levels.

In 1957 the International Cardiology Foundation was created as a lay organization with medical membership to promote lay education in cardiovascular disease and to raise funds for the advancement of cardiology throughout the world. In 1970 the International Cardiology Federation (ICF) was formed from the Foundation with the responsibility of raising funds for the scientific programs of the International Society of Cardiology and of stimulating the growth of national Cardiology Foundations. The formation of the International Cardiology Foundation was largely due to the imagination and enterprise of Dr Paul White. Mr Albert Baer of New York played a considerable part in fund raising at that time.

The membership of the International Cardiology Federation was composed of National Heart Foundations.

In 1970 at the Sixth World Congress of Cardiology in London the proposal for a merger between the ISC and the ICF was discussed. Dr White strongly stressed the wisdom of allowing experi-

enced laymen to assume responsibilities of fund raising and public relations. It was felt that the merger would greatly facilitate the work of both organizations and should provide a joint Society which would combine fund raising and educational activities with the promotion of research into the preventive, diagnostic, and therapeutic aspects of cardiovascular disease. However it was not until 1974 that arrangements for the merger were seriously discussed. In the intervening years the International Society of Cardiology was in receipt of generous support from the American Heart Association and from the Canadian Heart Foundation, in addition to subscriptions from many, though unfortunately not all national cardiac societies. Because of the financial problems of maintaining the basic organization necessary to promote its aims the ISC was not always able to allocate sufficient funds to maintain the work of the Scientific Councils and financial problems tended to multiply.

At the Seventh World Congress in Buenos Aires in September, 1974 the Assembly of the International Society of Cardiology agreed to the principle of a merger and directed that the details be worked out by a Long Range Planning Committee which was composed of representatives both of the ISC and the ICF. After numerous discussions in the ensuing months the terms of the merger were drawn up and the proposed statutes and bylaws were circulated to National Societies and Foundations. The statutes and bylaws did not differ materially from those already in existence. It was suggested that the merged organization should be essentially a medical/scientific body dedicated to the promotion of world cardiology by stimulation of research, teaching, lay and professional education and the encouragement of preventive aspects of cardiology. Fund raising and public relations would be important aspects also. The President would be medically qualified and although there would be a preponderance of medically qualified members on the Executive Board at all times there would be important members such as the First Vice President, Administration Secretary, the Treasurer, and Chairmen of the Public Education Committee who would not be medically qualified.

It was agreed that the merged organization should be called the International Society and Federation of Cardiology (ISFC) and a request was sent in mid 1976 to all National Societies and

## Sequence of cardiac changes in Duchenne muscular dystrophy\*

S B Heymsfield

T McNish

J V Perkins

J M Felner

Atlanta Ga

Pathologic examination of the heart in boys dying after age 12 with Duchenne muscular dystrophy (DMD) invariably shows marked left ventricular interstitial fibrosis and extensive replacement of myocardial fibers with connective tissue.<sup>1-4</sup> Heart failure is a common terminal manifestation of the disease. Clinical evidence of heart disease, however, is rare until shortly before death and even then is usually precipitated by pneumonia.

Cardiovascular physical examination is complicated by the presence of chest deformities, especially in boys over 12. Nevertheless, several possibly abnormal signs have been described. Tachycardia is a frequent finding, but its relationship to age and stage of skeletal muscle disease has not been defined. Left parasternal impulses occurred in about half of the 35 DMD boys in Perloff and colleagues' series, but were associated with normal right ventricular and pulmonary arterial pressures and were therefore attributed to chest deformity. Most DMD patients have a third heart sound, but up to age 30 this may be normal. Atrial gallops have been described in about one third of DMD patients.<sup>5</sup>

Chest x-ray examination reveals the straight thoracic spine and occasionally a pectus excavatum with resultant pancake heart. The skeletal

deformities make interpretation of the cardiac silhouette difficult, especially since they are most prominent in the end stages of the disease. Only two patients in Perloff and colleagues' series<sup>5</sup> had clear evidence of cardiomegaly; one of these died in cardiac failure shortly thereafter.

In contrast to physical examination and chest x-ray, the electrocardiogram reveals disturbances of electrical function in up to 90 per cent of patients<sup>1-5</sup> and has been used as a diagnostic criterion for DMD. Tall R waves are present in Lead V<sub>1</sub> and deep narrow q waves are found most frequently in Leads V and V<sub>4</sub>. These changes do not appear to be related to age or duration of disease or disability.

Echocardiography has been used by Kovick and associates<sup>6</sup> to study left ventricular wall motion in patients with different types of muscular dystrophy. These subjects had a significantly slower rate of diastolic relaxation of the left ventricular posterior wall than normal controls, although the degree of abnormality did not correlate with age, type or severity of dystrophy.

Cardiac catheterization has been useful in detecting latent cardiac dysfunction.<sup>1</sup> In Perloff and colleagues' series, abdominal compression in 70 per cent of subjects of unspecified age caused an abnormal rise in right atrial or right ventricular end diastolic pressure, possibly indicative of early cardiac dysfunction. Wahi and co-workers<sup>7</sup> found abnormal left ventricular dp/dt and end diastolic pressure in all of five Duchenne patients evaluated by left heart catheterization who had abnormal electrocardiograms. Again, however, age and extent of muscle disease were

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

Received for publication Sept. 13, 1976.

Accepted for publication Nov. 10, 1976.

Supported in part by Grants RR00039, GRSS-501, RR05364, and by a grant from the Muscular Dystrophy Association.

Reprint requests: E. H. Vignos, Jr., M.D., Department of Medicine, Emory University School of Medicine, Woodruff Medical Center, Atlanta, Ga. 30307.

Presented in part at the Southern Section of the AFERJ, July 24, 1976.

- tients. Chairman, Dr H Denolin (Belgium)  
 7 Council on Thrombosis and Haemostasis  
 Chairman, Dr M Hardisty (Great Britain)

These Councils usually have about 20 members who are drawn from all parts of the World

At its first meeting the Executive Board of the ISFC formulated an active program of fund raising scientific work, public education and sponsorship of world meetings. The ISFC of course, assumes responsibility for sponsorship of the World Congress of Cardiology in 1978. Advice on the Scientific Program and its organization is being given by the Chairmen of the Scientific Councils, the Chairman of the Scientific Board, and the President of the ISFC in collaboration with the organizers of the Congress in Tokyo.

The President of the ISFC will meet the Presidents of the Continental Societies in mid 1977 to discuss the mutual relationship of these Societies, the coordination and promotion of world meetings and collaboration in research. From this meeting it is hoped that better coordination of world events in cardiology will be achieved and better understanding of critical problems will result. It should be possible to delineate areas of special need for research, teaching and education so that rational allocation of funds can be achieved.

It is not surprising that, as the complexity of cardiological investigations and treatment increases, and as the exacting demands of advancing cardiovascular disease become more insistent, better cooperation and integration between international cardiological organizations become essential.

The Bulletins of the ISC and ICF have been combined in the Journal Heartbeat which will give news of the National Societies and Foundations of Cardiology, dates of meetings, reports of Scientific Councils and of public education events. Details of international meetings will be given regularly and in particular information about the Eighth World Congress of Cardiology in Tokyo in 1978 and of the progress of "World Hypertension Year, 1978" will appear from time to time.

"The Year of the Merger" 1977, should herald a new era in International Cardiology and the active support and encouragement of cardiac Societies and Foundations all over the world will be needed and appreciated as an essential requirement for success.

I am much indebted to Dr Vittorio Puddu, Past President of the ISC for data on history of the ISC published in the Bulletin of the ISC at the time of the Sixth World Congress of Cardiology in 1970. I am also indebted to Mme. Marianne de Figueiredo for material on the history of the ICF.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 765, Schenectady, N.Y. 12301, 518-374-4430, for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works, or for resale.

included in the examination Pericardial-epicardial echoes were identified with a low gain setting and then the gain was increased until the endocardial echo was located The record was obtained on heat sensitive paper at a speed of 50 mm per second using a Tektronix recorder In each record five different complexes were analyzed according to the method of Feigenbaum and the average values were calculated for the following variables diastolic internal diameter (mm) (LVIDd) systolic internal diameter (mm) (LVIDs) diastolic left atrial diameter (mm) (LADd) systolic left atrial diameter (mm) (LADs) diastolic aortic diameter (mm) (AOd) systolic aortic diameter (mm) (AOs) diastolic right ventricular internal diameter (mm) (RVIDd) diastolic posterior left ventricular wall thickness (mm) (WALLd) systolic posterior left ventricular wall thickness (WALLs) interventricular septal thickness (mm) (IV SEPT) and interventricular septal excursion (mm) (IVSE) In the three DMD patients with chest deformities the average value of the long (suprasternal view) and short (standard view) axis of the left atrium was used to calculate LADd and LADs The following were calculated from the echogram dimensions collected on each subject as follows

End diastolic volume = (LVIDd)  $\times$  1.05

End systolic volume = (LVIDs)  $\times$  1.05

Ejection fraction (EF) = stroke volume/end diastolic volume

Stroke index (SI) (cc/M) = end diastolic volume - end systolic volume/BSA

Cardiac index (CI) (liter/min/M) = heart rate  $\times$  (stroke index/1000)

Posterior LV wall excursion (mm) (WALLE) = maximum amplitude of systolic LV wall excursion

Per cent fractional shortening of the internal dimension from end diastole to end systole (%)

$$(\%LV) = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

Maximal systolic and diastolic endocardial velocities (SEVM DEVM) were determined according to the method of Kovick and associates which consists of drawing a tangent to the steepest portion of the systolic or diastolic endocardial excursion and measuring the slope in mm/sec The mean rate of circumferential fiber shortening (Vcf) was determined by measuring

Table 1 Comparison of DMD boys and control subjects matched according to age and BSA Values represent means  $\pm$  SD

|        | DMD<br>(N = 18) | Controls<br>(age matched)<br>(N = 18) | Controls<br>(BSA matched)<br>(N = 18) |
|--------|-----------------|---------------------------------------|---------------------------------------|
| Age    | 11.9 $\pm$ 3.3  | 11.8 $\pm$ 3.4                        | 10.1 $\pm$ 3.6                        |
| BSA(M) | 1.21 $\pm$ .31  | 1.34 $\pm$ .30                        | 1.21 $\pm$ .3 <sup>a</sup>            |

P < 0.1 for comparison of specified control v 1 with the corresponding DMD value

ejection time (LVET) from the carotid pulse tracing (time between initial carotid upstroke and the dicrotic notch at the completion of the echo cardiogram) and calculated according to the following equation

$$Vcf (\text{circ sec}) = \frac{LVIDd - LVIDs}{LVET \times LVIDd}$$

## Results

The results of matching the 18 DMD boys to 20 control subjects (Table I) reveal the differing relationship between age and body surface area (BSA) in the two groups Healthy boys matched with respect to age had a greater BSA than their DMD counterparts In contrast healthy subjects matched on the basis of BSA were younger than their DMD opposite members

The results of physical examination electrocardiogram chest x rays SCPh and its isoenzymes and echocardiography are presented for both controls and patients in Table II The results are given for either the age or BSA match whichever provided the higher correlation with the variable under consideration in the normal boys For the dimensions independent of age and BSA the age match is presented

The DMD boys were divided into early (age 4 to 10 years) and late DMD (age 9 to 17 years) on the basis of MMT ( $\geq$  50 per cent and < 50 per cent respectively) As Table II shows 26 types of cardiac measurement were made on each DMD child (physical examination one ECG two chest x ray one serum enzymes three echocardiography 19) In the normal boys serum enzyme levels were not measured

In control subjects eight of the 23 measurements were independent of age EQ/ER CI SI EF %LV IVSE Vcf and SEVM The other 15 measurements showed a significant (P < 0.05)



not specified. In addition, these procedures are invasive and medically unjustified in most DMD subjects.

Thus, while every patient with advanced DMD who has come to autopsy has had dystrophic heart disease, the natural history of this process during life has remained obscure because its progress is almost undetectable by conventional cardiovascular techniques. Echocardiography is a relatively new, noninvasive method utilizing reflected ultrasound for determining cardiac structure and function and is ideally suited to the study of dystrophic heart disease. This technique has been utilized in the present study to evaluate cardiac involvement in Duchenne muscular dystrophy patients.

### Materials and methods

The subjects were 18 boys with Duchenne dystrophy aged 4 to 17 years randomly selected from 45 under observation at the Emory Muscular Dystrophy Clinic, and 25 healthy boys. Diagnosis of Duchenne dystrophy was based on progressive weakness over a 3 to 7 year period of observation, particularly apparent in neck flexor, abdominal flexor, gluteus maximus and medius, middle trapezius and rhomboid musculature, pseudohypertrophy of the calves, onset of symptoms before age 8, positive family history in brothers and male maternal relatives, elevated serum concentrations of creatine phosphokinase, lactic dehydrogenase, and glutamic oxaloacetic transaminase, electromyographic evidence of myopathy, and confirmatory muscle biopsy in the patient or in an affected male relative.

Each DMD subject was hospitalized and underwent the following examinations: Cardiovascular physical examination, muscle function testing, ECG, chest x-ray, serum (iso)enzymes (CPK) and echocardiogram. The patient was then matched with two controls, one by age ( $\pm 1$  year) and one by body surface area ( $\pm 0.1$  M). Control subjects underwent as outpatients a series of examinations similar to those administered to the DMD boys.

**Physical examination.** A cardiovascular physical examination was performed. In order to quantify the degree of musculoskeletal involvement, manual muscle testing was performed on each patient and the result expressed as the per cent of normal muscle function remaining. Each

muscle group was assigned a numerical value as follows: 5 = Full range of motion against gravity with strong resistance; 4 = Full range of motion against gravity with moderate resistance; 3 = Full range of motion against gravity with other resistance; 2 = Full range of motion against gravity eliminated; 1 = No motion but visible or palpable contraction; and 0 = No visible or palpable contraction. The manual muscle test (MMT) score obtained by summing the weighted results of all muscle groups was divided by the total points obtainable for normal function and expressed as a per cent of normal. A score of 100 per cent represents normal function, while a score under 40 per cent represents severe musculoskeletal dysfunction.

**EKG.** A standard 12 lead electrocardiogram was done on each subject, and the following measurements made: (a) the ratio of the R to the S wave in Lead V<sub>1</sub> ( $R/S$  V<sub>1</sub>) was calculated and (b) q waves if present in Leads I, II, or V<sub>1</sub> were measured and expressed as a ratio to the R wave in that lead ( $Q/R$ ). The  $Q/R$  ratio in the three leads was then summed and expressed as a single value,  $\Sigma Q/R$ .

**Chest x-ray.** Standard six foot posteroanterior and lateral views were obtained for each patient and the two views were used to calculate heart volume.<sup>11</sup> This was then corrected for body surface area and expressed as the heart volume index (HV index).

**Enzymes.** Serum creatine phosphokinase (SCPK) concentration of each patient was determined. To gather information regarding a cardiac or skeletal source of this enzyme, SCPK was further separated into its isoenzyme fractions: MM CPK (skeletal muscle), BB CPK (brain), and MB CPK (heart).

**Echocardiogram.** The echocardiograms were performed with a Unirad echograph employing a 2.25 MHz, 0.5 inch diameter transducer with either a 10 cm or 7.5 cm focus. The transducer was placed in the fourth or fifth left intercostal space close to the sternum and the mitral valve was located. The transducer was then aimed inferiorly and laterally just below the anterior knuckle of the mitral valve in order to obtain simultaneous echoes of the interventricular septum and posterior left ventricular wall. If pectus excavatum or straight thoracic spine was present, an additional suprasternal approach was

included in the examination. Pericardial-epicardial echoes were identified with a low gain setting and then the gain was increased until the endocardial echo was located. The record was obtained on heat sensitive paper at a speed of 50 mm per second using a Tektronix recorder. In each record five different complexes were analyzed according to the method of Feigenbaum and the average values were calculated for the following variables: diastolic internal diameter (mm) (LVIDd), systolic internal diameter (mm) (LVIDs), diastolic left atrial diameter (mm) (LADd), systolic left atrial diameter (mm) (LADs), diastolic aortic diameter (mm) (AOD), systolic aortic diameter (mm) (AOS), diastolic right ventricular internal diameter (mm) (RVIDd), diastolic posterior left ventricular wall thickness (mm) (WALLd), systolic posterior left ventricular wall thickness (mm) (WALLs), interventricular septal thickness (mm) (IV SEPT), and interventricular septal excursion (mm) (IVSE). In the three DMD patients with chest deformities the average value of the long (suprasternal view) and short (standard view) axis of the left atrium was used to calculate LADd and LADs. The following were calculated from the echogram dimensions collected on each subject as follows:

End diastolic volume = (LVIDd)  $\times$  100  
 End systolic volume = (LVIDs)  $\times$  100  
 Ejection fraction (EF) = stroke volume/end diastolic volume  
 Stroke index (SI) (cc M) = end diastolic volume - end systolic volume/BSA  
 Cardiac index (CI) (liter/min/M) = heart rate  $\times$  (stroke index/1000)  
 Posterior LV wall excursion (mm) (WALLE) = maximum amplitude of systolic LV wall excursion  
 Per cent fractional shortening of the internal dimension from end diastole to end systole (%)

$$(\%LV) = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

Maximal systolic and diastolic endocardial velocities (SEVM DEVM) were determined according to the method of Kovick and associates<sup>3</sup> which consists of drawing a tangent to the steepest portion of the systolic or diastolic endocardial excursion and measuring the slope in mm/sec. The mean rate of circumferential fiber shortening (Vcf) was determined by measuring

**Table 1** Comparison of DMD boys and control subjects matched according to age and BSA. Values represent means  $\pm$  SD

|         | DMD<br>(N = 18) | Controls<br>(age matched)<br>(N = 19) | Controls<br>(BSA matched)<br>(N = 16) |
|---------|-----------------|---------------------------------------|---------------------------------------|
| Age     | 11.9 $\pm$ 3.3  | 11.8 $\pm$ 3.4                        | 10.1 $\pm$ 3.6                        |
| BSA (M) | 1.71 $\pm$ .31  | 1.34 $\pm$ .30                        | 1.71 $\pm$ .37                        |

P < 0.05 r comparison of specified control value with the corresponding DMD value

ejection time (IVET) from the carotid pulse tracing (time between initial carotid upstroke and the diastolic notch at the completion of the echocardiogram) and calculated according to the following equation:

$$Vcf (\text{circ sec}^{-1}) = \frac{LVIDd - LVIDs}{LVET \times LVIDd}$$

### Results

The results of matching the 18 DMD boys to 20 control subjects (Table 1) reveal the differing relationship between age and body surface area (BSA) in the two groups. Healthy boys matched with respect to age had a greater BSA than their DMD counterparts. In contrast healthy subjects matched on the basis of BSA were younger than their DMD opposite members.

The results of physical examination, electrocardiogram, chest x rays, SCPh, and its isoenzymes and echocardiography are presented for both controls and patients in Table II. The results are given for either the age or BSA match, whichever provided the higher correlation with the variable under consideration in the normal boys. For the dimensions independent of age and BSA, the age match is presented.

The DMD boys were divided into early (age 4 to 10 years) and late DMD (age 9 to 17 years) on the basis of MMT ( $\geq$  50 per cent and < 50 per cent respectively). As Table II shows, 26 types of cardiac measurement were made on each DMD child (physical examination, one ECG, two chest x rays, one serum enzyme, three echocardiography, 19). In the normal boys, serum enzyme levels were not measured.

In control subjects, eight of the 23 measurements were independent of age: EQ/ER, CI, SI, FF, %LV, IVSF, Vcf, and SEVM. The other 15 measurements showed a significant ( $P < 0.05$ )

Table II Summary of cardiac measurements in DMD<sup>a</sup>

|                      | Match        | Total    |           |      |     |           |        | Early DMD |           |      |     |           |      |
|----------------------|--------------|----------|-----------|------|-----|-----------|--------|-----------|-----------|------|-----|-----------|------|
|                      |              | Controls |           |      | DMD |           |        | Controls  |           |      | DMD |           |      |
|                      |              | Pairs    | $\bar{X}$ | S.D. | N   | $\bar{X}$ | S.D.   | Pairs     | $\bar{X}$ | S.D. | N   | $\bar{X}$ | S.D. |
|                      |              |          |           |      |     |           |        |           |           |      |     |           |      |
| Physical examination |              |          |           |      |     |           |        |           |           |      |     |           |      |
| HR                   | age          | 18       | 64.0      | 10.6 |     | 90.5†     | 13.1   | 9         | 73.1      | 11.5 |     | 91        | 54   |
| Electrocardiogram    |              |          |           |      |     |           |        |           |           |      |     |           |      |
| R/S V                | age          | 18       | 46        | 35   |     | 132†      | 81     | 9         | 67        | 37   |     | 112       | 5    |
| ΣQ/ΣR                | age          | 18       | 04        | 07   |     | 37†       | 42     | 9         | 07        | 1    |     | 37        | 5    |
| Chest x ray          |              |          |           |      |     |           |        |           |           |      |     |           |      |
| HV index (cc/M)      | age          | 18       | 323.8     | 55.7 |     | 390.2†    | 128.0  | 9         | 300.0     | 51.0 |     | 315.9     | 6    |
| Serum enzymes        |              |          |           |      |     |           |        |           |           |      |     |           |      |
| SCPK (units)         |              |          |           |      | 18  | 3961.1    | 3158.0 |           |           |      | 9   | 5110      | 330  |
| MM CPK (units)       |              |          |           |      | 16  | 3403.0    | 2820.0 |           |           |      | 8   | 5061.0    | 371  |
| MB CPK (units)       |              |          |           |      | 16  | 502.8     | 849.6  |           |           |      | 8   | 941.0     | 173  |
| Echocardiogram       |              |          |           |      |     |           |        |           |           |      |     |           |      |
| A Anatomy            |              |          |           |      |     |           |        |           |           |      |     |           |      |
| LV                   | WALLd (mm)   | BSA      | 18        | 6.5  | 1.0 |           | 6.6    | 1.0       | 9         | 5.4  | 1.4 |           | 5.9  |
|                      | WALLs (mm)   | BSA      | 18        | 11.2 | 2.3 |           | 10.4†  | 1.6       | 9         | 10.3 | 1.9 |           | 9.8  |
|                      | IV Sept (mm) | BSA      | 18        | 7.7  | 1.5 |           | 7.2    | 1.5       | 9         | 7.1  | 1.5 |           | 6.5  |
|                      | IVId (mm)    | BSA      | 18        | 41.2 | 6.1 |           | 40.2   | 5.4       | 9         | 39.3 | 6.9 |           | 31.9 |
| LA                   | IVId (mm)    | BSA      | 18        | 27.1 | 3.9 |           | 28.7   | 5.2       | 9         | 26.7 | 4.3 |           | 90   |
|                      | IADd (mm)    | BSA      | 18        | 18.6 | 3.8 |           | 17.8   | 5.0       | 9         | 16.7 | 3.4 |           | 100  |
|                      | LADs (mm)    | BSA      | 18        | 24.4 | 4.7 |           | 24.7   | 5.4       | 9         | 23.0 | 3.7 |           | 91.3 |
|                      | AOd (mm)     | BSA      | 18        | 21.1 | 3.2 |           | 20.9   | 1.6       | 9         | 20.2 | 2.5 |           | 90   |
| AO                   | AOs (mm)     | BSA      | 18        | 23.8 | 3.3 |           | 23.3   | 2.3       | 9         | 21.1 | 3.2 |           | 21.3 |
|                      | RVIDd (mm)   | BSA      | 8         | 11.3 | 3.9 |           | 9.6    | 3.2       | —         |      |     |           |      |
| B Function           |              |          |           |      |     |           |        |           |           |      |     |           |      |
| SI (cc beat/M)       | age          | 18       | 45.1      | 13.7 |     | 37.0†     | 9.3    | 9         | 40.0      | 12.3 |     | 30.4      | 9    |
| CI (L/min/M)         | age          | 18       | 3.0       | 9    |     | 24        | 1.3    | 9         | 3.2       | 9    |     | 3.6       | 10   |
| EF                   | age          | 18       | 71        | 0.0  |     | 63†       | 08     | 9         | 72        | 04   |     | 6         | 04   |
| LV (cc)              | age          | 18       | 33.9      | 3.8  |     | 28.9†     | 4.7    | 9         | 34.0      | 3.9  |     | 31.1      | 2    |
| WALLE (mm)           | BSA          | 18       | 9.7       | 1.6  |     | 7.5       | 1.6    | 9         | 9.2       | 9    |     | 6.7       | 14   |
| IVSE (mm)            | BSA          | 16       | 7.0       | 9    |     | 6.1†      | 1.0    | 9         | 7.2       | 5    |     | 5.7       | 10   |
| DFVM (mm/sec)        | age          | 18       | 127.6     | 20.7 |     | 80.5†     | 27.4   | 9         | 116.5     | 17.3 |     | 89.6†     | 110  |
| SEVM (mm/sec)        | age          | 18       | 42.2      | 7.6  |     | 38.8      | 7.9    | 9         | 34.8      | 10.7 |     | 42.6      | 34   |
| V (cm/sec)           | age          | 15       | 1.08      | 13   |     | 1.04      | 18     | 7         | 1.10      | 14   |     | 1.00      | 13   |

P values by paired t test indicate statistical difference

P < .1

1P < .05

2P < .01

3P < .001

<sup>a</sup> Includes those pairs in whom both members had an RVIDd of technically good quality and if normal chest configuration was present

<sup>b</sup> Manual muscle test  $\geq$  50%

<sup>c</sup> Manual muscle test < 50%

linear relationship both with age and with BSA. The regression equations describing the relation of 14 of these variables with age or BSA are given in Table III for control subjects and DMD youngsters.

When the entire DMD group was compared with the entire control group 11 of the 23 measurements showed a statistically significant difference: HR, R/S V, ΣQ/ΣR, HV index, WALLS, SI, EF, LV, WALLE, IVSE, and

DEVM. Contrastingly when this comparison was made in the patients with early DMD and their matched controls only six of 23 cardiac measurements different significantly: heart rate, R/S V, ΣQ/ΣR, WALLE, IVSE, and DEVM. In the late DMD subgroup these six variables showed even more marked deviations from normal and in addition significant differences from matched controls had now appeared in five other cardiac indices: HV index, EF, LV, SI, WALLE, and Vef.

| Late DMD |           |     |     |           |      |
|----------|-----------|-----|-----|-----------|------|
| Controls |           |     | DMD |           |      |
| Pairs    | $\bar{x}$ | SD  | N   | $\bar{x}$ | SD   |
| ■        | 57°       | 8   | 89  | 31        | 88   |
| 9        | 8         | 7   | 150 | 10        |      |
| 9        | 03        | 01  | 36  | 55        |      |
| 9        | 347       | 51  | 476 | 1160      |      |
|          |           |     | 9   | 1990      | 910  |
|          |           |     | 8   | 1450      | 870  |
|          |           |     | 8   | 1005      | 1130 |
| 9        | 7         | 14  | 13  | 17        |      |
| 9        | 172       | 74  | 116 | 11        |      |
| 9        | 87        | 13  | 9   | 14        |      |
| 9        | 431       | 50  | 475 | 59        |      |
| 9        | 786       | 9   | 313 | 56        |      |
| 9        | 706       | 34  | 188 | 55        |      |
| 9        | 764       | 49  | 27  | 69        |      |
| 9        | 770       | 71  | 1   | 1         |      |
| 9        | 46        | 78  | 246 | 13        |      |
| 9        | 467       | 157 | 388 | 98        |      |
| 9        | 8         |     | 32  | 10        |      |
| 9        | ■         | 06  | 60  | 09        |      |
| 9        | 338       | 38  | 766 | 53        |      |
| 9        | 107       | 70  | 151 | 18        |      |
| 8        | 68        | 17  | 63  | 10        |      |
| 9        | 1387      | 287 | 714 | 311       |      |
| 9        | 386       | 48  | 475 | 38        |      |
| 8        | 106       | 17  | 93  | 18        |      |

A more detailed view of several indices which were significantly abnormal in the DMD group is given in Fig 1 HR R/S V  $\Sigma Q/\Sigma R$  SCPK and MB CPK WALLE and DEVM. In these graphs every DMD boy is shown together with his matched control.

Fig 1 A HR heart rate showed a significant inverse relation with age in the controls. In DMD an inverse relation with age was also evident but for a given age the heart rate of DMD boys was faster than those of their matched controls.

Fig 1 B R/S V in normal boys the ECG R/S ratio in Lead V decreased with age. In DMD patients no such age relationship was evident. Furthermore 78 per cent (14/18) of the DMD

boys had a greater R/S V ratio than the upper limit of normal for their age.

Fig 1 C  $\Sigma Q/\Sigma R$  this value was  $< 0.2$  in 89 per cent of normal boys and did not vary with age. In DMD  $\Sigma Q/\Sigma R$  exceeded 0.2 in 65 per cent of patients and exceeded the value of the age matched control in 72 per cent of cases. No relation to age was evident.

Fig 1 D Muscle enzymes were abnormally elevated in all DMD patients. There was a progressive decline in total and cardiac (MB) CPK with loss of muscle function (MMT).

Fig 1 E LV wall excursion increased with BSA in normal boys. Although a similar relationship held in DMD patients the latter group generated a subnormal line in which WALLE was lower for any given BSA. In 89 per cent (16/18) of DMD boys WALLE was lower than that of the BSA matched control.

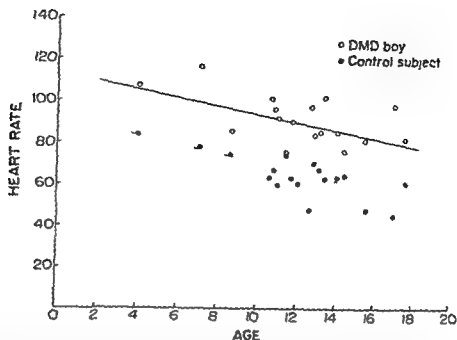
Fig 1 F DEVM increased with age in normal subjects but in DMD this function decreased with age. In 89 per cent (16/18) of DMD boys the DEVM was lower than in the age matched control.

In order to determine if there was a significant relationship between cardiac involvement and skeletal muscle disease severity we performed regression analysis of each of these 11 indices against MMT. In no case was there a significant correlation ( $P < 0.05$ ) although  $\Delta DEVM$  ( $\Delta DEVM = \text{value expected for age } [724 + 49(\text{age})] - \text{observed DEVM}$ ) was of borderline significance ( $r = 0.4$   $P = 0.6$ ).

The echogram of a 12 year old DMD boy (MMT 42 per cent) and his BSA matched control are presented in Fig 2. The systolic excursion of the LV endocardium (WALLE) is reduced and the maximal systolic and diastolic endocardial velocities are slower in the DMD boy.

## Discussion

**Summary of the findings** Two technical factors concerning echocardiography should be considered before physiological significance is attributed to the observations made in DMD boys. The first problem is that echocardiographic measurements of volume and function are based on an assumed geometric model of the heart pectus excavatum (PE) might compress the ventricle and invalidate these calculations. In the present investigation only three subjects had PE



Figs 1A through 1E Examples of the cardiovascular abnormalities found in DMD subjects. See Results section for further details. A Heart rate versus age in DMD boys and age matched control subject. The regression equations for all 25 control subjects and for 18 DMD boys are presented in Table III

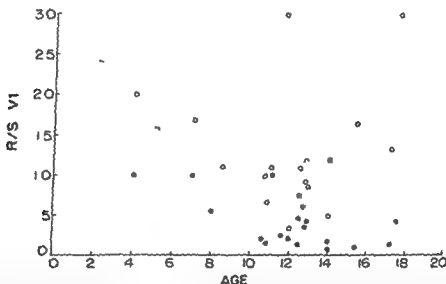


Fig 1B ECG R/S ratios in Lead V in DMD boys and age matched control subjects. The dashed line represents the upper limits of normal for the R/S ratio in Lead V. (The upper limits of normal are derived from Ziegler R. Electrocardiographic standards in infants and children. Springfield, Ill. 1961. Charles C Thomas, Publisher.)

(LDMD group) and furthermore six of the 11 abnormal indices were present in EDMD when no skeletal deformities were yet evident. Thus PE did not contribute to most of the abnormal cardiac findings described. The second consideration is that segmental myocardial disease could make echocardiographic calculations unreliable. In DMD, however, the disease process as observed at autopsy usually has a symmetrical distribution with diffuse connective tissue and fat replacement and normal coronary arteries.<sup>11</sup>

Accordingly, we have calculated the various echo dimensions by the conventional equations.<sup>12</sup> If, however, the early cardiac lesions have an asymmetric or segmental distribution, our echocardiographic calculations will be correspondingly inaccurate. Pending future clarification of this question, the echo dimensions in Table II are therefore only tentative.

The present investigation confirms the report of Kovick and colleagues<sup>13</sup> that DEV is subnormal in subjects with muscular dystrophy.

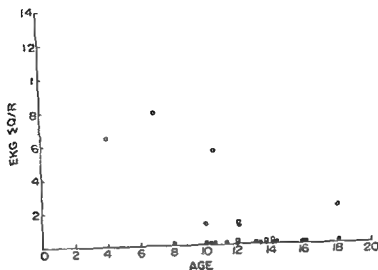


Fig 1C ECG S/Q/R in DMD boys and age matched control subjects

Table III Regression equations\* relating age or body surface area to cardiovascular dimensions

|            | Control Subjects |                      |      |        | DMD Subjects |                      |      |        |
|------------|------------------|----------------------|------|--------|--------------|----------------------|------|--------|
|            | N                | Equation             | r    | P†     | N            | Equation             | r    | P†     |
| Heart rate | 25               | = 89.8 - 2.1 (age)   | 0.73 | < .001 | 18           | = 111.8 - 1.78 (age) | .45  | = .05  |
| HV index   | 25               | = 195.5 + 11.7 (age) | 0.80 | < .001 | 18           | = 189.6 + 1.1 (age)  | 0.64 | < .05  |
| WALLd      | 25               | = 2.67 + 3.2 (BSA)   | 0.79 | < .001 | 18           | = 3.14 + 2.8 (age)   | 0.69 | < .01  |
| WALLs      | 25               | = 5.27 + 4.64 (BSA)  | 0.78 | < .001 | 18           | = 6.0 + 3.7 (BSA)    | 0.63 | < .01  |
| IV SEPT    | 25               | = 4.78 + 2.39 (BSA)  | 0.60 | < .01  | 18           | = 3.64 + 3.0 (BSA)   | 0.69 | < .01  |
| LVIDd      | 25               | = 22.0 + 15.0 (BSA)  | 0.79 | < .001 | 18           | = 26.5 + 11.5 (BSA)  | 0.66 | < .01  |
| LVIDs      | 25               | = 13.5 - 10.7 (BSA)  | 0.78 | < .001 | 18           | = 18.5 + 9.3 (BSA)   | 0.45 | = .05  |
| LADd       | 25               | = 4.8 + 2.4 (BSA)    | 0.60 | < .01  | 18           | = 6.8 + 9.3 (BSA)    | 0.60 | < .05  |
| LADs       | 25               | = 12.9 + 9.5 (BSA)   | 0.79 | < .001 | 18           | = 14.1 + 9.2 (BSA)   | 0.57 | < .05  |
| AOd        | 25               | = 11.3 + 8.0 (BSA)   | 0.77 | < .001 | 18           | = 15.3 + 4.5 (BSA)   | 0.69 | < .01  |
| AOs        | 25               | = 14.5 + 7.6 (BSA)   | 0.77 | < .001 | 18           | = 17.2 + 4.8 (BSA)   | 0.88 | < .001 |
| RVIDd      | 18               | = 4.20 + 5.9 (BSA)   | 0.66 | < .001 | 11           | = -7 + 11.7 (BSA)    | 0.5  | < .1   |
| WALLE      | 25               | = 6.1 + 3.0 (BSA)    | 0.73 | < .001 | 18           | = 4.7 + 2.7 (BSA)    | .55  | < .05  |
| DEVM       | 25               | = 72.4 + 4.9 (age)   | 0.79 | < .001 | 18           |                      |      | Not    |

\*Regression equation determined by the method of least squares

†P &lt; .05 correlation coefficient regression equation

‡N = regression equation not significant (P &gt; .1)

including DMD. Our present investigation extends this observation by defining the relationship of DEVM to age in both DMD and normal boys and by identifying associated changes in Vcf SEVM WALLS and EF.

The present data define two stages in the natural history of Duchenne heart disease. Patients with early DMD compared to matched controls (Table IV) have a significantly ( $P < .05$ ) faster heart rate, greater R/S ratio in V<sub>1</sub>, and q wave magnitudes elevated total and MB CPK, diminished echogram LV wall and IV septal excursions, and slower DEVM. Boys with late

DMD (Table IV) are characterized by the continued presence of these functional abnormalities and now show in addition increased x-ray heart volume index, lower total and MB CPK, and subnormal echogram EF. LV DEVM and circumferential fiber shortening throughout the course of DMD heart disease while the above mentioned functional abnormalities appear and progress, the anatomic dimensions of left ventricular wall and septal thickness remain normal.

Our goal must be to understand the mechanism for each of these abnormalities in cardiac behavior. Towards this end, the possible mechanisms

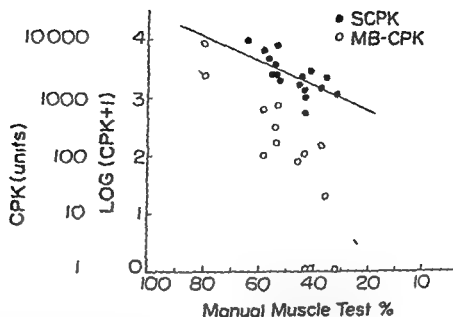


Fig 1D Total (SCPK) and MB CPK isoenzyme levels in DMD subjects versus age. The regression equation for SCPK and MB CPK are  $\log (\text{SCPK} + 1) = 2.42 + 0.021 (\text{MMT})$   $r = 0.1$   $P < 0.001$  and  $\log (\text{MB-CPK} + 1) = 1.24 + 0.07 (\text{MMT})$   $r = 0.69$   $P < 0.05$

Table IV Summary of cardiovascular examination in DMD patients

|  | Early DMD | Late DMD |
|--|-----------|----------|
| <b>Clinical examination</b>              |           |          |
| 1 Heart rate                             | ++        | ++       |
| 2 Pectus excavatum                       |           | +        |
| <b>Electrocardiogram</b>                 |           |          |
| 1 R-S V                                  | ++        | ++       |
| 2 q waves                                | ++        | ++       |
| <b>Chest x ray</b>                       |           |          |
| 1 Heart volume index                     | +         | ++       |
| <b>Serum enzymes</b>                     |           |          |
| 1 CPK                                    | +++       | ++       |
| 2 MB CPK                                 | ++        | +        |
| <b>Echocardiogram</b>                    |           |          |
| <b>A Anatomy</b>                         |           |          |
| 1 LV diastolic wall thickness            | →         | →        |
| 2 LV systolic wall thickness             | →         | →        |
| 3 LV internal dimensions                 | →         | →        |
| <b>B Function</b>                        |           |          |
| 1 Cardiac output                         | →         | →        |
| 2 Stroke volume                          | +         | +        |
| 3 Ejection fraction                      | +         | ++       |
| 4 % change in LV internal dimension      | +         | ++       |
| 5 LV wall excursion                      | ++        | ++       |
| 6 IV septal excursion                    | ++        | +        |
| 7 Maximal systolic endocardial velocity  | +         | +        |
| 8 Maximal diastolic endocardial velocity | ++        | +++      |
| 9 Circumferential fiber shortening       | +         | ++       |

↑ = increased above control boys  
→ = no change  
↓ = decreased below control boys.

for each abnormal cardiovascular index identified in this study will be considered below.

Possible mechanisms for each of the cardiac findings

Tachycardia was a feature of both early and late stages confirming earlier observation in DMD boys of unspecified age.<sup>1</sup> Two mechanisms have been postulated.

1 A circulating chronotropic agent eg thyroid hormone(s) or catecholamines has been suggested<sup>1</sup> although recent studies have failed to support this view.<sup>1</sup>

2 An alternative hypothesis is that an early impairment in cardiac contractility caused a reflex tachycardia. The present echocardiogram data support this mechanism by showing that impaired contractile function generally accompanied the tachycardia. In both early and late DMD WALLE and DEVM were decreased compared to normal, furthermore in late DMD EF Vcf and SEVM were subnormal while LV index was increased. All of these changes suggest defective contractility.

EKG changes in this study as in others were present in > 90 per cent of DMD boys.<sup>1</sup> The most prevalent of these increased values for R/S V<sub>1</sub> and S/Q<sub>1</sub> R were evident even in the youngest patients evaluated. Four possible mechanisms have been suggested for the increased R/S V<sub>1</sub>, RV or septal hypertrophy, impaired conduction and loss of posterior left ventricular electrical forces. The present echo data provide direct

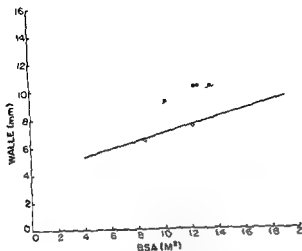


Fig 1E Posterior left ventricular wall excursion (WALLE) versus body surface area (BSA) in DMD patients and BSA matched control boys. The regression equations for all 25 control subjects and for 18 DMD boys are presented in Table III.

evidence against the first two hypotheses because RV and septal dimensions were normal. The q wave phenomenon has been ascribed to diffuse necrotic zones creating electrically silent regions. The present data shed no light on the pathogenesis of the abnormal q waves.

Heart size by x-ray appeared to be excessive in late DMD. The chest deformities of late DMD introduce a possible technical error in radiographic heart volume calculations. Nevertheless, since the apparent cardiomegaly of late DMD was associated with several echocardiographic signs of impaired contractile function, it probably represented the dilatation of early heart failure. Because LV and septal wall thickness were not increased, the cardiomegaly evidently manifested dilatation rather than hypertrophy. The absence of LV hypertrophy in the echocardiogram dimensions of advanced DMD is not surprising in view of the extensive loss of muscle cells and deposition of fibrous tissue which are regularly present at autopsy.

**Serum enzymes.** The recognition of latent cardiomyopathy in DMD boys would be easier if the dysfunctional myocardial cell released a specific enzyme into the serum. An obvious candidate for such a test is MB CPK. This isoenzyme is specific for heart in both normal and DMD subjects.

Total CPK was markedly elevated in early DMD and declined progressively with age. This

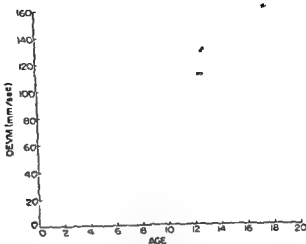


Fig 1F Maximal diastolic endocardial velocity (DEV) versus age in DMD young men and in age matched healthy boys. The regression equations for all 20 control subjects and for 18 DMD boys are presented in Table III.

confirms the findings of Pearce and colleagues and Okinaka and associates<sup>19</sup> who attributed the high initial value to diseased but viable skeletal muscle and the progressive decline to a continuing loss of skeletal muscle fibers from which CPK is derived. The present study reveals a similar course for MB CPK. The possibility arises therefore that this enzyme could serve as a qualitative indicator of the progression of cardiac DMD. High MB CPK might indicate the early cardiac stage and a low or absent value might show late disease. The validity of this notion awaits future testing.

**Echocardiogram abnormalities in early DMD.** (Table IV) were limited to a decrease in WALLE, a smaller IVSE and a diminished DEV. Two possible mechanisms for these early abnormalities are (1) an adaptation to the tachycardia found in DMD boys and (2) impaired myocardial contractility.

1 With regard to the first view, the tachycardia of exercise or adrenergic stimulation is associated with increased WALLE and DEV. WALLE and DEV were reduced in DMD. Thus this explanation is untenable.

2 The second hypothesis proposes that decreased myocardial contractility results from myocardial fibrosis or from a molecular impediment to the contraction-relaxation process. Cullen and Fulthorpe<sup>20</sup> have demonstrated hypercontracted muscle fibers in DMD skeletal



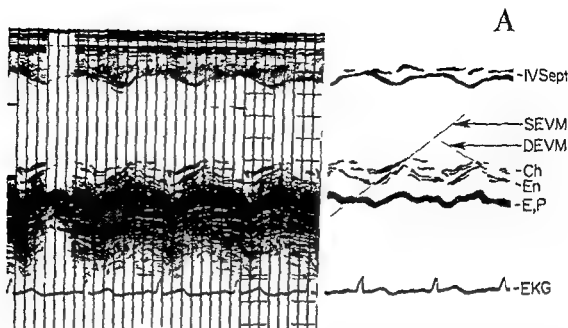


Fig 2A Echogram of a 13 year old boy with DMD showing simultaneous echoes of the interventricular septum (IVSept) chordae tendineae (Ch) left ventricular endocardium (En) and the epi pericardium (E,P). Maximal systolic endocardial velocity (SEVM) and maximal diastolic endocardial velocity (DEVM) are derived from the slope of a tangent drawn to the steepest portion of the systolic or diastolic endocardial excursion.

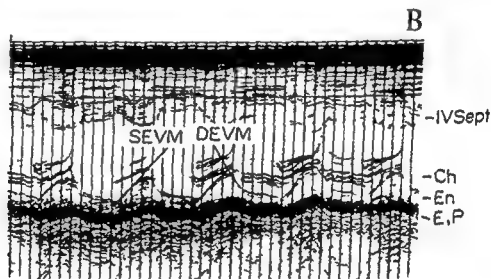


Fig 2B Note the diminished posterior left ventricular wall excursion (WALLE) and decreased maximal systolic endocardial velocity (SEVM) and maximal diastolic endocardial velocity (DEVM) of the DMD boy in Fig. 2A compared to his BSA matched control subject.

muscle and inferred a defective relaxation of myofibrillae possibly related to excess calcium content of mitochondria. Kovick and co workers,<sup>13</sup> who initially described the subnormal echo DEVM in DMD subjects suggested this abnormality could manifest an interruption in the normal release and uptake of calcium within sarcoplasmic reticulum during contraction and relaxation. Since the binding of calcium to sarcoplasmic reticulum has in fact been shown to be abnormal *in vitro* in preparations from human and animal dystrophic muscle,<sup>14</sup> the subnormal

WALLE and DEVM of early and late DMD could manifest an inherited disorder in Ca mediated contraction-relaxation.

**Echocardiogram abnormalities in late DMD** (Table IV). In addition to the early changes discussed above the following disturbances now appear: subnormal EF, SEVM, and Vcf. These three changes unequivocally indicate impaired systolic performance of the heart in ejecting blood. The underlying mechanisms could include three abnormalities known to be present in the late stages of DMD: loss of myocardial muscle

cells accumulation of fibrous tissue in the myocardium and deconditioning. A contribution by chest wall deformity is unlikely because a recent study<sup>1</sup> by catheterization in non dystrophic patients with more advanced pectus excavatum than the present DMD boys showed no abnormality in supine contractile function.

**Possible clinical applications.** The present data have two possible applications.

1. The lack of a statistically significant correlation between most echocardiographic indices and MMT (see Results section) suggests that DMD may progress at different rates in heart and in skeletal muscle. Therefore the extent of heart involvement cannot be deduced by examining musculature of trunk and extremities. Moreover cardiac physical examination, chest x ray and ECG fail to reveal the progression of Duchenne heart disease because the ECG changes do not evolve with age, chest deformity distorts the cardiac silhouette as in endocardial fibrosis, deposition of connective tissue may partially counteract the tendency of the failing heart to dilate. Consequently congestive failure tends to be unpredictable in DMD. Echocardiography reveals the progressive changes in cardiac function during the life of the DMD child and should indicate when decompensation is imminent.

2. Carriers of the DMD gene sometimes have mildly elevated SCPK and slight changes in muscle histology, but identification of the carrier state is still uncertain. Echocardiography showed impaired WALLE and DEVM in our youngest DMD boys whose MMT was virtually normal. If as discussed above these changes reflect an inherited disorder of the contraction-relaxation process in muscle cells, the echocardiogram may have some use in the detection of carriers of the DMD gene.

### Summary

Boys with Duchenne muscular dystrophy (DMD) rarely have clinical evidence of myocardial dysfunction during life. Nevertheless congestive heart failure is a frequent terminal event and autopsy invariably shows dystrophic myocardial involvement. Little is known regarding the progression of heart functional abnormalities in boys with DMD from birth to death. Therefore we have examined the hearts of 18 DMD boys aged 4 to 15 years with the following non invasive methods: cardiovascular physical examination, elec-

trocardiography, chest x ray, serum enzymes and echocardiography. Control subjects were 25 normal boys matched to their DMD counterparts by age and by body surface area.

The dystrophic patients were divided into early (N = 9) and late (N = 9) DMD according to manual muscle testing of skeletal muscles. In early DMD six of 23 cardiac indices differed from control boys; in the late stage an additional five indices became abnormal.

Early DMD was characterized by these abnormalities: tachycardia, large ECC R/S ratio in  $V_1$ , augmented q wave voltages in Leads I, II and  $V_3$ , of the ECG, diminished contractile excursion of the left ventricular posterior wall (LVPW) and interventricular septum and decreased rate of relaxation of the LVPW.

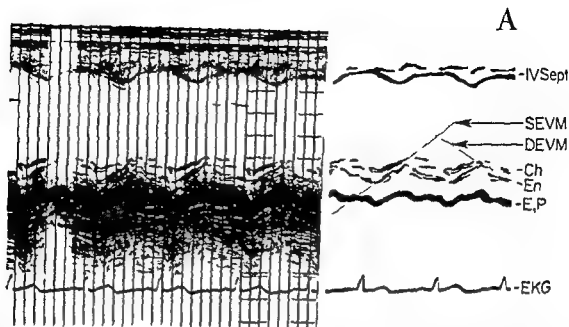
In late DMD additional cardiac abnormalities appeared: enlarged heart volume by x ray, reduced cardiac ejection fraction, diminished change in left ventricular diameter from diastole to systole, reduced maximal systolic endocardial velocity and decreased rate of circumferential fiber shortening as detected in the echocardiogram.

Most of the cardiac abnormalities were revealed only by echocardiography which is thus shown to be a sensitive method for monitoring the progression of cardiac dystrophy during the life span of the DMD child.

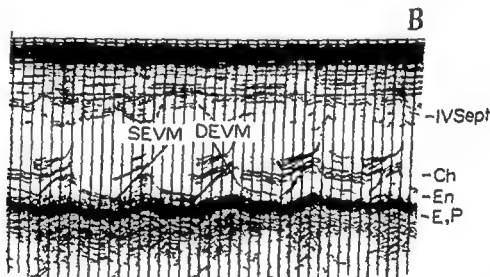
The authors are indebted to Drs. Daniel Rudman, Ellen Fuller, Donald Nutter and Michael Kutner for their critical review of the manuscript.

### REFERENCES

1. Perloff J K, de Leon Jr A C and O'Doherty D. The cardiomyopathy of progressive muscular dystrophy. *Circulation* 33:675, 1966.
2. Gilroy J, Cahalan J L, Berman R and Newman M. Cardiac and pulmonary complications in Duchenne's progressive muscular dystrophy. *Circulation* 27:484, 1963.
3. Fisher E R and Danowski T S. Electromicroscopy in the study of disorders of skeletal muscle. In Sommers S C, editor. *Pathology Annual*. New York 19:4. Appleton Century Crofts Division of Prentice Hall Inc. New York pp 345-384.
4. Bevans M. Changes in the musculature of the gastrointestinal tract and in the myocardium in progressive muscular dystrophy. *Arch Pathol* 40:15, 1945.
5. Boas E P and Lowenburg H. The heart rate in progressive muscular dystrophy. Studies with the cardio tachometer. *Arch. Intern. Med* 47:316, 1931.
6. Leth A, Njard B and Christoffersen J. Cardiac involvement in Duchenne's progressive muscular dystrophy. Clinical and electrocardiographic findings in 23 cases. *Dan Med Bull* 20:137, 1973.



**Fig 2A** Echogram of a 13 year old boy with DMD showing simultaneous echoes of the interventricular septum (IVSept) chordae tendineae (Ch) left ventricular endocardium (En) and the epicardium (E,P). Maximal systolic endocardial velocity (SEVM) and maximal diastolic endocardial velocity (DEVM) are derived from the slope of a tangent drawn to the steepest portion of the systolic or diastolic endocardial excursion



**Fig 2B** Note the diminished posterior left ventricular wall excursion (WALLE) and decreased maximal systolic endocardial velocity (SEVM) and maximal diastolic endocardial velocity (DEVM) of the DMD boy in Fig 2A compared to his BSA matched control subject

muscle and inferred a defective relaxation of myofibrillar possibly related to excess calcium content of mitochondria. Kovick and co-workers<sup>11</sup> who initially described the subnormal echo DEVM in DMD subjects suggested this abnormality could manifest an interruption in the normal release and uptake of calcium within sarcoplasmic reticulum during contraction and relaxation. Since the binding of calcium to sarcoplasmic reticulum has in fact been shown to be abnormal *in vitro* in preparations from human and animal dystrophic muscle,<sup>12</sup> the subnormal

WALLE and DEVM of early and late DMD could manifest an inherited disorder in Ca mediated contraction-relaxation.

**Echocardiogram abnormalities in late DMD** (Table IV) In addition to the early changes discussed above the following disturbances now appear subnormal FF, SEVM and Vef. These three changes unequivocally indicate impaired systolic performance of the heart in ejecting blood. The underlying mechanisms could include three abnormalities known to be present in the late stages of DMD: loss of myocardial muscle

# Ondine's Curse Hemodynamic response to diaphragm pacing (electrophrenic respiration)

Rene A Langou MD  
Lawrence S Cohen MD  
David Sheps MD  
Steven Wolfson MD  
William W L Glenn MD  
*New Haven Conn*

Alveolar hypoventilation secondary to abnormal central nervous system control of respiration is an uncommon pathological condition. Severinghaus and Mitchell, who reported three patients believed to have sustained damage to the medullary carbon dioxide chemoreceptors as the result of neurosurgical procedures, were the first to apply the name Ondine's Curse to this syndrome.

Burnoff and collaborators, 25 years ago, applied temporarily artificial respiration to several patients with ventilatory insufficiency secondary to bulbar poliomyelitis. The technique of artificial respiration consisted of electrical stimulation of the phrenic nerve; they termed this technique electrophrenic respiration (EPR). Long term stimulation of the phrenic nerve became possible with the successful development in our clinic of a cardiac pacemaker powered by a radiofrequency transmitter.<sup>1</sup>

Electrophrenic respiration or, as we have preferred to call it, diaphragm pacing,<sup>2</sup> has been investigated at Yale University School of Medicine since 1963 and it has been applied successfully to patients since 1966. This re-

port presents the hemodynamic changes produced by diaphragm pacing in a selected series of patients with Ondine's Curse (Alveolar Hypoventilation).

## Materials and methods

Eight patients with Ondine's Curse were studied following implantation of a radiofrequency electrophrenic respirator.

Table I gives the clinical profile of these eight patients. There were six males and two females. Their ages ranged from 37 to 54 years with a mean of 49 years. The presenting symptoms were congestive heart failure in eight patients, somnolence in seven, lethargy in three, polycythemia in three, and headaches in one patient. Two of the patients were moderately obese. On the electrocardiogram there were three instances of right bundle branch block, two of right ventricular hypertrophy, two of right axis deviation, and two of right atrial hypertrophy. Only two of the eight patients displayed a normal electrocardiographic pattern.

The chest x-ray was normal in only one patient. The others demonstrated a variety of abnormal radiological findings: Right ventricular enlargement, dilatation of the pulmonary artery, generalized cardiomegaly, and pulmonary vascular changes compatible with pulmonary hypertension were seen alone or in combination.

The probable etiology of this syndrome in these eight patients was primary hypoventilation in three, electroshock therapy in two, and in one

From the Department of Medicine, Section of Cardiology and Department of Surgery, Section of Cardiothoracic Surgery, Yale University School of Medicine, New Haven, Conn.

Aided by grants USPHS H104751, USPHS HL 14119, USPHS RR00130, and the Culpeper Foundation.

Received for publication Sept. 23, 1976.

Accepted for publication May 1, 1977.

Reprint requests: Rene A. Langou, MD, Yale University School of Medicine, 333 Cedar Street, S-100, New Haven, Conn. 06510.

- 7 Slucka C The electrocardiogram in Duchenne progressive muscular dystrophy *Circulation* 38 933 1968
- 8 Schott J, Jacobi M and Wald M A Electrocardiographic patterns in the differential diagnosis of progressive muscular dystrophy *Am J Med Sci* 229 517 1975
- 9 Skyring A and McKusick V A Clinical genetic and electrocardiographic studies in childhood muscular dystrophy *Am J Med Sci* 242 534 1961
- 10 Wahi P L, Mahindra S and Khattri H N Left heart hemodynamics in progressive muscular dystrophy *Indian Heart J* 26 286 1974
- 11 Sundermeyer J F, Gudbjarnason S, Wendt V E, den Bakker P B and Bing R J Myocardial metabolism in progressive muscular dystrophy *Circulation* 24 1348 1961
- 12 Gallani S, Danowski T S and Fisher D S Muscular dystrophy. Catheterization studies indicating latent congestive heart failure *Circulation* 17 583 1958
- 13 Keats T E and Enge I P Cardiac mensuration by the cardiac volume method *Radiology* 85 850 1963
- 14 Feigenbaum H *Echocardiography* Philadelphia 1972 Lea & Febiger Publishers 239 pp
- 15 Kovick R B, Fogelman A M, Abbasi A S, Peter, J B and Pearce M L Echocardiographic evaluation of posterior left ventricular wall motion in muscular dystrophy *Circulation* 52 447 1975
- 16 Danowski R S, Bastiani R M, McWilliams F D, Mateer F M and Greenman L Muscular dystrophy IV Endocrine studies *Am J Dis Child* 91 356 1956
- 17 Ronan J A, Perloff J K, Bowen P J and Mann O The vectorcardiogram in Duchenne's progressive muscular dystrophy *Am Heart J* 84 688 1972
- 18 Pearce J M S, Pennington R J and Walton J V Serum enzyme studies in muscle disease. Part II. Creatine kinase activity in muscular dystrophy and other myopathic and neuropathic disorders *J Neurol Neurosurg Psychiatry* 27 96 1964
- 19 Okinaka S, Kumagai H, Ebashi S, Sugita H, Muro H, Toyokura Y and Fujie Y Serum creatine phosphokinase activity in progressive muscular dystrophy and neuromuscular diseases *Arch Neurol* 45 90 1961
- 20 Fogelman A M, Abbasi A S, Pearce M L and Kattus A A Echocardiographic study of the abnormal motion of the posterior left ventricular wall during angina pectoris *Circulation* 48 905 1973
- 21 Krausz R F and Kennedy J W Ultrasonic determination of left ventricular wall motion in normal man. Studies at rest and after exercise *Am Heart J* 79 36 1970
- 22 Cullen M J and Fulthorpe J J Stages in the breakdown in Duchenne muscular dystrophy *J Neurol Sci* 24 179 1975
- 23 Takagi A, Schotland D L and Rowland L P Sarcoplasmic reticulum in Duchenne muscular dystrophy *Arch Neurol* 28 380 1973
- 24 McCollum W B, Crow C, Hangaya S, Bajusz E and Schwartz A Calcium binding by cardiac relaxin system isolated from myopathic Syrian hamsters (Strains 146, 8262 and 4054) *J Mol Cell Cardiol* 1 445 1970
- 25 de Leon Jr A C, Perloff J K, Twigg H and Mink M The straight back syndrome. Clinical cardiovascular manifestations *Circulation* 32 193 1965
- 26 Pearson C M Muscular dystrophy. Review and recent observations *Am J Med* 35 677 1963

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following statement signed by each author: The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

# **PROTOCOL**

REST BREATHING ROOM AIR

↓  
EPR (diaphragm pacing) FOR 10 MINUTES

↓  
REST BREATHING ROOM AIR FOR 10 MINUTES

↓  
100% OXYGEN INHALATION FOR 10 MINUTES

↓  
EPR PLUS OXYGEN FOR 10 MINUTES

**Fig 1** Pulmonary and systemic arterial pressures, systemic arterial blood gases, and saturation and cardiac output were obtained during each period. EPR = electrophrenic respiration alias diaphragm pacing.

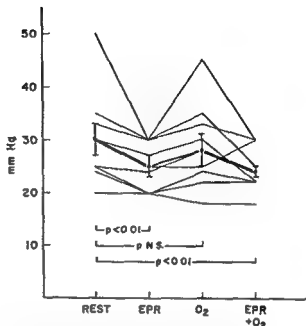
Data were analyzed for significance of change by the paired Student *t* test.

## **Results**

**Pulmonary artery pressure** There was a fall in mean pulmonary artery pressure on diaphragm pacing from 30 mm Hg at rest to 25 mm Hg ( $p < 0.01$ ) (Fig 2). The decrease was most prominent in cases with pulmonary hypertension. Administration of 100% oxygen by inhalation did not significantly affect mean pulmonary artery pressure and oxygen inhalation plus pacing did not decrease mean pulmonary artery pressure further than did pacing alone. There was no significant effect of 100 per cent oxygen by inhalation on pulmonary vascular resistance in these patients.

There was a similar fall in systolic pulmonary artery pressure on pacing from 44 mm Hg at rest to 30 mm Hg ( $p < 0.02$ ) (Fig 3). Oxygen inhalation did not significantly change the peak systolic pressure and pacing plus oxygen inhalation lowered the systolic pulmonary artery pressure to 33 mm Hg. Mean pulmonary capillary wedge pressure (Table II) averaged 15 mm Hg at rest and decreased to 12 mm Hg with pacing to 14 mm Hg with oxygen inhalation and to 12 mm Hg oxygen plus pacing. This change was not statistically significant. Arteriole vascular resistance (Table II) was calculated in only five of the eight patients and in these the resting average of 289 dyne/sec/cm<sup>5</sup> fell to 203 dyne/sec/cm<sup>5</sup> with pacing ( $p < 0.05$ ) and to 229 dyne/sec/cm<sup>5</sup> with pacing plus oxygen inhalation ( $p < 0.07$ ).

# **MEAN PULMONARY ARTERY PRESSURE**



**Fig 2** Individual patient values and group means  $\pm$  standard error of the mean for mean pulmonary artery pressure in eight patients with central hypoventilation syndrome during rest, EPR (diaphragm pacing) with O<sub>2</sub> (oxygen inhalation) and with EPR + O<sub>2</sub> (diaphragm pacing plus oxygen inhalation).

**Table II** Hemodynamic profile of patients with Ondine's Curse

|      | No of patients | Rest            | EPR             | O               | EPR + O         |
|------|----------------|-----------------|-----------------|-----------------|-----------------|
| CO†  | 5              | 4.15 $\pm$ 0.07 | 3.93 $\pm$ 0.19 | 3.83 $\pm$ 0.28 | 3.83 $\pm$ 0.44 |
| SAP  | 8              | 137 $\pm$ 4     | 139 $\pm$ 5     | 141 $\pm$ 5     | 130 $\pm$ 5     |
| DAP  | 8              | 77 $\pm$ 4      | 75 $\pm$ 4      | 70 $\pm$ 9      | 74 $\pm$ 4      |
| PCW  | 8              | 15 $\pm$ 0.3    | 12 $\pm$ 0.6    | 14 $\pm$ 0.4    | 12 $\pm$ 0.5    |
| PAVR | 5              | 289 $\pm$ 15    | 203 $\pm$ 30    | 290 $\pm$ 42    | 229 $\pm$ 54    |

All measurements are expressed as  $\bar{x} \pm$  standard error ( $p < 0.05$  by *t* test compared with  $\bar{x}$  in control measurements).  
 †Abbreviations: CO = cardiac output (expressed as liters per minute);  
 DAP = diastolic aortic pressure (in mm Hg); EPR = electrophrenic respiration; EPR + O = electrophrenic respiration plus 100 per cent oxygen inhalation; O = 100 per cent oxygen inhalation;  
 PAVR = pulmonary artery vascular resistance (in dynes/sec/cm<sup>5</sup>);  
 PCW = pulmonary capillary wedge pressure (in mm Hg);  
 SAP = systolic aortic pressure (in mm Hg).

**Aortic pressure** Recorded during the four states, aortic pressure showed a minimal but statistically significant fall in systolic pressure with pacing and with pacing plus oxygen inhalation. Diastolic pressure and heart rate did not

Table 1 Clinical profile of eight patients with Ondine's Curse

| YHH Unit No       | Sex | Age | Symptoms                                      | Electrocardiogram | Chest x ray  | Probable etiology                        |
|-------------------|-----|-----|---|-------------------|--|--|
| 1 E D<br>78 55 08 | F   | 54  | Somnolence<br>Lethargy<br>CHF<br>Polycythemia | RVH               | Enlargement of right ventricle   | Primary hypoventilation                  |
| 2 S F<br>82 11 00 | M   | 47  | Somnolence<br>Lethargy<br>CHF                 | Normal            | Normal   | Electroshock therapy 3 months previously |
| 3 A D<br>80 83 22 | M   | 54  | Lethargy                                      | RBBB              | Enlargement of pulmonary artery  | Head trauma 10 years previously          |
| 4 M S<br>84 20 18 | F   | 47  | Somnolence<br>CHF<br>Polycythemia             | RAH<br>RVH        | Enlargement of pulmonary artery and right ventricle  | Viral encephalitis 38 years previously   |
| 5 J F<br>85 85 11 | M   | 60  | Somnolence<br>CHF                             | Normal            | Generalized cardiomegaly and enlargement of pulmonary artery                                   | Poliomyelitis 40 years previously        |
| 6 W R<br>86 59 19 | M   | 53  | Somnolence<br>CHF<br>Polycythemia             | RAH<br>RAD        | Generalized cardiomegaly and pulmonary vascular changes comparable with pulmonary hypertension | Primary hypoventilation                  |
| 7 L T<br>86 01 13 | M   | 37  | Somnolence<br>CHF<br>Headaches                | RBBB              | Enlargement of right ventricle   | Primary hypoventilation                  |
| 8 R S<br>84 06-16 | M   | 52  | Somnolence<br>CHF                             | RBBB              | Enlargement of pulmonary artery  | Electroshock therapy 1 year previously   |

Abbreviations CHF = congestive heart failure F = female M = male RAD = right axis deviation RAH = right atrial hypertrophy  
RBBB = right bundle branch block RVH = right ventricular hypertrophy

each of the remaining three trauma to the head viral encephalitis and poliomyelitis. Studies on all patients clearly established that alveolar hypoventilation was on the basis of malfunction of central ventilatory control.<sup>15</sup>

The patients underwent cardiac catheterization according to the protocol outlined in Fig 1. In each state listed pulmonary artery pulmonary wedge and systemic arterial pressures were measured through catheters placed in the pulmonary artery and central aorta. To obtain pulmonary wedge pressure the catheter was passed from the pulmonary artery to the pulmonary capillary position and later withdrawn to its original place in the pulmonary artery. The catheters were connected to Statham P23Db pressure transducers. Reference point for pressure measurement was at the level of the patient's midchest in the supine position. The pressure tracings were obtained using a multichannel recorder.\*

Cardiac output was measured by injecting indocyanine (green dye) into the pulmonary artery and sampling from the central aortic catheter. The arterial blood traversed the densitometer that was connected with a recorder and integrator.\*

Arterial blood gases were measured in each state sequentially at rest after ten minutes of diaphragm pacing during a second period of rest after ten minutes of inhalation of two liters of 100 per cent oxygen and finally after ten minutes more of pacing.

Artificial respiration was accomplished using a radiofrequency diaphragm pacemaker. The characteristics of the pacemaker have been reported previously.\*<sup>12</sup>

All hemodynamic measurements were done between five days and 18 months after the implantation of the electrophronic respirator. One patient underwent two separate studies one month and then one year after implantation.

## ARTERIAL OXYGEN TENSION

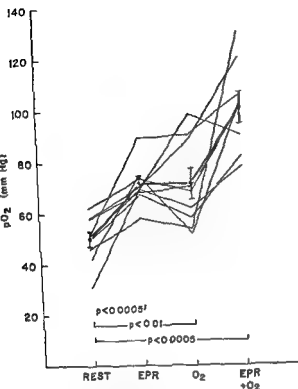


Fig 5 Individual patient values and group means  $\pm$  standard error for arterial oxygen tension in eight patients with central hypoventilation syndrome

carbon dioxide tension increased arterial pH fell and systolic systemic pressure rose though insignificantly. Finally when oxygen inhalation and pacing were used together the changes in all measured parameters were similar to those observed with pacing alone.

It is evident that the patients in our series had pulmonary hypertension at rest and their pulmonary artery pressure diminished concomitant with the correction accomplished by pacing of hypoxemia hypercapnea and acidosis. In the presence of chronic hypoxic pulmonary disease there is evidence of pulmonary vasoconstriction.<sup>11</sup> Jameson<sup>12</sup> postulated that hypoxemia leads to vasoconstriction in the pulmonary pre capillary capillary and post capillary beds. When hypoxemia alone was corrected in our patients the pulmonary artery pressure did not decrease suggesting that there must be factors other than hypoxemia contributing to pulmonary hypertension. Von Euler and Liljestrand<sup>13</sup> found that an

## ARTERIAL CARBON DIOXIDE TENSION

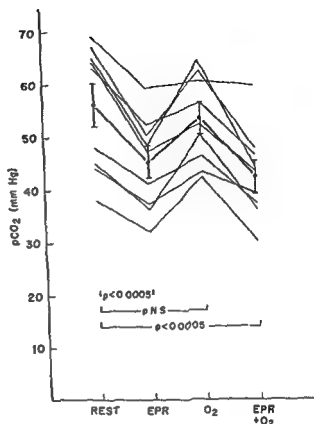


Fig 6 Individual patient values and group means  $\pm$  standard error for arterial carbon dioxide tension in eight patients with central hypoventilation syndrome

increase in carbon dioxide tension raises the pulmonary artery pressure. Liljestrand<sup>13</sup> later attributed such elevation of pressure to an increase in hydrogen ion concentration. Bergofsky and colleagues<sup>14</sup> demonstrated that changes in pH influence vasoconstriction in the pulmonary vasculature.

Since the correction of hypercarbia could only be accomplished by the use of diaphragm pacing we cannot distinguish between the effect on the pulmonary artery pressure of lowering the carbon dioxide tension or of raising the pH. Calculated pulmonary arteriolar vascular resistance decreased only on pacing. The mechanism for this was improvement in ventilation due to aeration of unventilated alveoli resulting in correction of hypoxemia hypercapnea and acidosis. In addition there may have been an improvement in ventilation perfusion ratio in previously hypoven-



## SYSTOLIC PULMONARY ARTERY PRESSURE

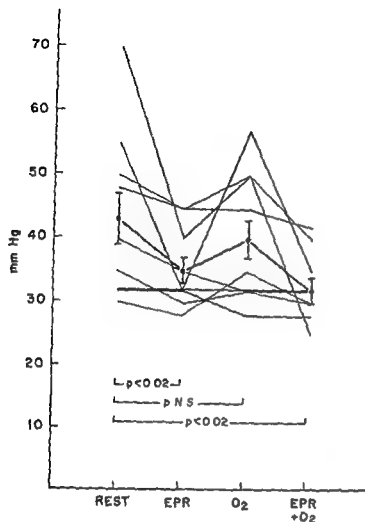


Fig 3 Individual patient values and group means  $\pm$  standard error of the mean for systolic pulmonary artery pressure in eight patients with central hypoventilation syndrome during the four states: Rest, EPR (diaphragm pacing),  $O_2$  (oxygen inhalation) and EPR +  $O_2$  (diaphragm pacing plus oxygen inhalation).

show significant change on any intervention (Table II).

**Cardiac output** This remained unchanged during the four states in five of the patients in whom it was measured (Table II).

**Arterial blood gases** The arterial pH averaged  $7.39 \pm 0.01$  mm Hg during rest, increasing to  $7.46 \pm 0.01$  mm Hg during pacing (Fig 4). Oxygen inhalation also tended to normalize the pH giving a mean value of  $7.41 \pm 0.01$  mm Hg. Oxygen plus pacing changed the pH to an alkalotic level of  $7.49 \pm 0.01$  mm Hg. The arterial  $PO_2$  averaged 50 mm Hg at rest increasing to 70 mm Hg ( $p < 0.0005$ ) with pacing (Fig 5). Oxygen inhalation alone yielded a mean tension of 70 mm Hg. Pacing plus oxygen inhalation yielded an  $O_2$  tension of 100 mm Hg. Pacing significantly

## ARTERIAL pH

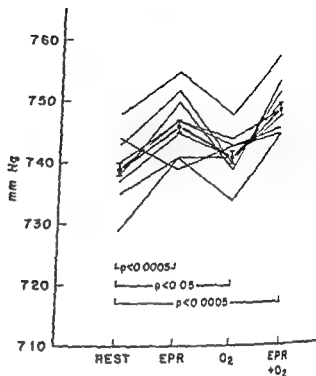


Fig 4 Individual patient values and group means  $\pm$  standard error for arterial pH in eight patients with central hypoventilation syndrome.

lowered the  $P_{CO_2}$  from a level of 55 mm Hg at rest to 44 mm Hg ( $p < 0.0005$ ) (Fig 6).

## Discussion

Since the early studies of Sarnoff and co-workers<sup>4</sup> on temporary electrical stimulation of the phrenic nerve, several studies from our clinic have shown that an effective exchange of oxygen and carbon dioxide can be achieved for prolonged periods using the radiofrequency diaphragm pacemaker.<sup>13</sup> The present report documents the hemodynamics and blood gas alterations produced in eight patients with primary alveolar hypoventilation. The clinical features manifested by most of these patients are similar to the one described by Richter and associates.<sup>14</sup>

Pacing of these eight patients caused a fall in mean pulmonary arterial and systemic arterial pressure, a fall in arterial carbon dioxide tension and a rise in arterial oxygen tension and pH. Calculated pulmonary arteriolar vascular resistance also decreased with pacing. When oxygen inhalation was used alone, arterial oxygen tension rose but mean pulmonary artery pressure and calculated pulmonary arteriolar vascular resistance remained unchanged. Arterial carbon

# Measurement of the circulatory effects of dobutamine a new inotropic agent in patients following cardiac surgery

G R J Lewis MRACP MRCP  
P A Poole Wilson MD MRCP  
T A Angerpointer MD  
A E Farnsworth FRCS  
H T Williams FRCS  
D J Coltart MD MRCP FACC

London England

The treatment of a patient with a low cardiac output is often disappointing and the approach to management controversial. The use of pharmacological and physical agents to support and improve left ventricular function following low cardiac output states is at present a subject of considerable reappraisal. Guidelines as to whether invasive methods such as balloon counterpulsation or medical pharmacological therapy should be employed have not been clearly defined. In most hospitals medical management has the advantage that it is readily applicable. With the introduction of peripheral vasodilators—salbutamol nitroglycerine phentolamine—for this clinical situation the role of inotropic agents—isonoprenaline adrenaline dopamine has been criticized and become less clear. To obviate some of the theoretical disadvantages of available inotropic agents new compounds have been synthesized.

Dobutamine hydrochloride is a recently introduced cardio-selective synthetic catecholamine with a structure similar to isoprenaline and dopamine. Early studies with this drug revealed that it had potent inotropic activity but

compared with other catecholamines it caused less increase in heart rate. It had little effect on peripheral beta receptors and peripheral resistance was little altered. As a result of this the reduction in diastolic coronary perfusion pressure seen with isoprenaline and the elevated systolic pressures frequently caused by adrenaline and dopamine do not occur with this drug.

Unlike dopamine dobutamine does not rely for part of its action on the release of stored catecholamines which may be severely depleted after cardiopulmonary bypass when inotropic therapy is often indicated. Animal studies have shown that the increase of cardiac output produced by dobutamine improves flow to the coronary and iliac beds but causes only a minimal change in renal blood flow. Studies on myocardial infarction in dogs have demonstrated that dobutamine causes less increase in infarct size than other inotropic agents and suggest that this could be due to a combination of slower heart rate coronary vasodilation and maintenance of aortic diastolic coronary perfusion pressure. Such studies suggest therefore that dobutamine is a potentially useful drug in the treatment of low output states.

The object of this study was to compare the hemodynamic effects of dobutamine and isoprenaline in patients after cardiopulmonary bypass. In addition we describe a new approach to intensive monitoring of the hemodynamic state

From the Departments of Cardiology and Thoracic Surgery, St. Thomas Hospital, London, England.  
Received for publication October 13, 1976.  
Accepted for publication March 19, 1977.  
Requests for reprints to Dr. J. H. Coltart, Department of Cardiology, St. Thomas Hospital, London, SE1 7GL, England.

tilated portions of the lung. The present study indicates that patients with Ondine's Curse have a component reversible by the factors which lead to their pulmonary hypertension. Thus, diaphragm pacing in such patients should effect substantial relief of cor pulmonale.

### Summary

The hemodynamic response to diaphragm pacing was studied in eight patients with Ondine's Curse. It was shown that such pacing could lower the pulmonary artery pressure while correction of hypoxemia alone could not. It was demonstrated that on pacing calculated pulmonary arteriolar resistance decreased and there was normalization of arterial blood gases. The mechanism for these changes was improved alveolar ventilation.

### REFERENCES

- Severinghaus J W and Mitchell R A. Ondine's Curse—failure of respiratory center automaticity while awake. *Clin Res* 10:122 1962.
- Sarnoff S J, Hardenbergh E and Whittenberger J L. Electrophrenic respiration. *Am J Physiol* 155:1 1958.
- Sarnoff S J, Hardenbergh E and Whittenberger J L. Electrophrenic respiration. *Science* 108:482 1958.
- Sarnoff S J, Gaensler F H and Maloney J V. Electrophrenic respiration. The effectiveness of contralateral ventilation during activity of one phrenic nerve. *J Thorac Surg* 19:929 1950.
- Glenn W W L, Mauro A, Longo E, Livveter P H and Mackay F J. Remote stimulation of the heart by radiofrequency transmission. Clinical application to a patient with Stokes Adams syndrome. *N Engl J Med* 281:948 1969.
- Fusenberg L, Mauro A and Glenn W W L. Transistorized pacemaker for remote stimulation of the heart by radiofrequency transmission. *IRE Trans Biomed Electronics* 8:23 1961.
- Glenn W W L, Hageman H H, Mauro A, Fusenberg L, Flanagan S and Harvard M. Electrical stimulation of excitable tissue by radio frequency transmission. *Surg* 160:338 1964.
- Eisenberg L, Mauro A, Glenn W W L and Harward M. Radiofrequency stimulation as a means of a diaphragmatic tool. *Science* 147:578 1965.
- van Heckeeren D and Glenn W W L. Electrophrenic respiration by radiofrequency induction. *J Thorac Cardiovasc Surg* 52:635 1966.
- Judson J P and Glenn W W L. Radio-frequency electrophrenic respiration. *J A M A* 203:1033 1961.
- Glenn W W L, de Leuchtenberg N, van Heckeeren D, W Sato G, Holcomb W G and Pabson A. Heart block in children. Treatment with a radiofrequency pacemaker. *J Thorac Cardiovasc Surg* 58:661 1969.
- Glenn W W L, Holcomb W G, Gee J B and Ruzic R. Central hypoventilation. Long term ventilation assistance by radiofrequency electrophrenic respiration. *Surg* 172:755 1970.
- Glenn W W L, Holcomb W G, Hogan J F, Mason I, Gee J B L, Motoyama F H, Hum C S, Forbes R S and Forbes G. Diaphragm pacing by radiofrequency transmission in the treatment of chronic respiratory insufficiency. Present status. *J Thorac Cardiovasc Surg* 66:700 1973.
- Forbes G S, Glenn W W L and Langou R C. Ventilation. Radio-pirometry in electrophrenic respiration. *Diaphragm Pacing Surgery* 75:392 1974.
- Richter T, West J R and Fishman A P. The syndrome of alveolar hypoventilation and diminished sensitivity of the respiratory center. *N Engl J Med* 256:1165 1957.
- Colton T. *Statistics in medicine*. Boston 1974. Little Brown & Company p 131.
- Nye R L. Alveolar hypoventilation and cor pulmonale secondary to damage to the respiratory center. *Am J Cardiol* 8:416 1961.
- Jameson A G. Diffusion of gases from alveoli to precapillary arteries. *Science* 139:626 1963.
- Von Euler V R and Liljestrand G. Observation on the pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 12:301 1946.
- Liljestrand G. Chemical control of the distribution of pulmonary blood flow. *Acta Physiol Scand* 44:1 1959.
- Bergofsky E H, Lehr D E and Fishman A P. The effect of changes in hydrogen ion concentration on the pulmonary circulation. *J Clin Invest* 41:1499 1962.

# Measurement of the circulatory effects of dobutamine, a new inotropic agent, in patients following cardiac surgery

G R J Lewis MRACP MRCP  
P A Poole Wilson MD MRCP  
T A Angerpointer MD  
A F Farnsworth FRCS  
B T Williams FRCS  
D J Coltart MD MRCP FACC  
London England

The treatment of a patient with a low cardiac output is often disappointing and the approach to management controversial. The use of pharmacological and physical agents to support and improve left ventricular function following low cardiac output states is at present a subject of considerable reappraisal. Guidelines as to whether invasive methods such as balloon counterpulsation or medical pharmacological therapy should be employed have not been clearly defined. In most hospitals medical management has the advantage that it is readily applicable. With the introduction of peripheral vasodilators—salbutamol nitroprusside phenolamine for this clinical situation the role of inotropic agents—isonrenaline adrenaline dopamine has been criticized and become less clear. To obviate some of the theoretical disadvantages of available inotropic agents new compounds have been synthesized.

Dobutamine hydrochloride is a recently introduced cardioselective synthetic catecholamine with a structure similar to isoprenaline and dopamine. Early studies with this drug revealed that it had potent inotropic activity but

compared with other catecholamines it caused less increase in heart rate. It had little effect on peripheral beta receptors and peripheral resistance was little altered. As a result of this the reduction in diastolic coronary perfusion pressure seen with isoprenaline and the elevated systolic pressures frequently caused by adrenaline and dopamine do not occur with this drug.

Unlike dopamine dobutamine does not rely for part of its action on the release of stored catecholamines which may be severely depleted after cardiopulmonary bypass when inotropic therapy is often indicated. Animal studies have shown that the increase of cardiac output produced by dobutamine improves flow to the coronary and iliac beds but causes only a minimal change in renal blood flow. Studies on myocardial infarction in dogs have demonstrated that dobutamine causes less increase in infarct size than other inotropic agents and suggest that this could be due to a combination of slower heart rate coronary vasodilation and maintenance of aortic diastolic coronary perfusion pressure. Such studies suggest therefore that dobutamine is a potentially useful drug in the treatment of low output states.

The object of this study was to compare the hemodynamic effects of dobutamine and isoprenaline in patients after cardiopulmonary bypass. In addition we describe a new approach to intensive monitoring of the hemodynamic state

From the Department of Cardiology and Cardiovascular Surgery at Thomas Hospital, London, England.  
Received for publication October 13, 1977.  
Accepted for publication March 1, 1978.  
Reprint requests to Dr. J. H. C. Lewis, Department of Cardiology, Thomas Hospital, London SE5, England.

tilated portions of the lung. The present study indicates that patients with Ondine's Curse have a component reversible by the factors which lead to their pulmonary hypertension. Thus diaphragm pacing in such patients should effect substantial relief of cor pulmonale.

### Summary

The hemodynamic response to diaphragm pacing was studied in eight patients with Ondine's Curse. It was shown that such pacing could lower the pulmonary artery pressure while correction of hypoxemia alone could not. It was demonstrated that on pacing calculated pulmonary arteriolar resistance decreased and there was normalization of arterial blood gases. The mechanism for these changes was improved alveolar ventilation.

### REFERENCES

- Severinghaus J W and Mitchell R A Ondine's Curse—failure of respiratory center automaticity while awake. *Clin Res* 10:122 1962
- Sarnoff S J Hardenbergh E and Whittenberger J L Electrophrenic respiration. *Am J Physiol* 155:1 1948
- Sarnoff S J Hardenbergh E and Whittenberger J L Electrophrenic respiration. *Science* 108:482 1948
- Sarnoff S J Gaensler E H and Maloney J V Electrophrenic respiration. The effectiveness of contralateral ventilation during activity of one phrenic nerve. *J Thorac Surg* 19:929 1950
- Glenn W W L Mauro A Longo E Lavietes P H and Mackay F J Remote stimulation of the heart by radiofrequency transmission. Clinical application to a patient with Stokes Adams syndrome. *N Engl J Med* 261:948 1959
- Eisenberg L Mauro A and Glenn W W L Transistorized pacemaker for remote stimulation of the heart by radiofrequency transmission. *IRE Trans Biomed Electronics* 8:253 1961
- Glenn W W L Hageman H H Mauro A Eisenberg L Flamigan S and Harvard M Electrical stimulation of excitable tissue by radio frequency transmission. *Am J Surg* 160:338 1964
- Eisenberg L Mauro A Glenn W W L and Harvard J H Radiofrequency stimulation: a research and clinical tool. *Science* 147:578 1965
- van Heeckeren D and Glenn W W L Electrophrenic respiration by radiofrequency induction. *J Thorac Cardiovasc Surg* 52:655 1966
- Judson J P and Glenn W W L Radio-frequency electrophrenic respiration. *J A M A* 203:1031 1967
- Glenn W W L de Leuchtenberg N van Heeckeren D W Sato G Holcomb W G and Palouk A M block in children. Treatment with a radiofrequency pacemaker. *J Thorac Cardiovasc Surg* 58:61 1967
- Glenn W W L Holcomb W G Gee J B and Rich R Central hypoventilation. Long term ventilation assistance by radiofrequency electrophrenic respiration. *Am Surg* 172:700 1970
- Glenn W W L Holcomb W G Hoan J F Wada J Gee J B Motoyama E H Kim C S Pore R S and Forbes G Diaphragm pacing by radiofrequency transmission in the treatment of chronic obstructive pulmonary insufficiency. Present status. *J Thorac Cardiovasc Surg* 66:505 1973
- Forbes G S Glenn W W L and Lange R C No. 133 Radiospirometry in electrophrenic respiration. *Diaphragm pacing Surgery* 75:388 1974
- Richter T West J R and Fishman A P The syndrome of alveolar hypoventilation and diurnal sensitivity of the respiratory center. *N Engl J Med* 256:1165 1957
- Colton T. *Statistics in medicine*. Boston 1946. Little Brown & Company p 131
- Maey R L Alveolar hypoventilation and cor pulmonale secondary to damage to the respiratory center. *Am J Cardiol* 8:416 1961
- Jameson A G Diffusion of gases from alveoli to precapillary arteries. *Science* 139:876 1963
- Von Euler V R and Liljestrand G Observations on pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 12:301 1946
- Liljestrand G Chemical control of the distribution of pulmonary blood flow. *Acta Physiol Scand* 44:195 1958
- Bergofsky E H Lehr D E and Fishman A P The effect of changes in hydrogen ion concentration on the pulmonary circulation. *J Clin Invest* 41:1497 1962

Table 1 Hemodynamic values during dobutamine and isoprenaline infusion

| Patient and amount infusion | HR |     | BP  |        | LAP    |     | CI   |      | SVI  |    | PRI |    | SWI |    | % VA |     |     |
|-----------------------------|----|-----|-----|--------|--------|-----|------|------|------|----|-----|----|-----|----|------|-----|-----|
|                             | D  | I   | D   | I      | D      | I   | D    | I    | D    | I  | D   | I  | D   | I  | D    | I   |     |
| HB                          | a  | 80  | 80  | 126/67 | 126/66 |     | 2.5  | 2.5  | 31   | 31 | 33  | 33 | 35  | 35 | 100  | 100 |     |
|                             | b  | 8   | 88  | 124/60 | 120/57 |     | 2.5  | 2.5  | 29   | 31 | 36  | 27 | 32  | 32 | 109  | 107 |     |
|                             | c  | 86  | 100 | 136/60 | 128/54 |     | 2.55 | 3.3  | 30   | 33 | 33  | 24 | 35  | 36 | 121  | 123 |     |
|                             | d  | 91  | 110 | 140/60 | 101/48 |     | 2.8  | 3.5  | 31   | 31 | 31  | 19 | 37  | 29 | 131  | 140 |     |
| CB                          | a  | 105 | 100 | 107/74 | 107/78 | 10  | 10   | 3.2  | 3.4  | 30 | 33  | 27 | 26  | 35 | 39   | 100 | 100 |
|                             | b  | 106 | 107 | 107/75 | 110/78 | 9   | 10   | 3.3  | 3.6  | 31 | 35  | 26 | 25  | 36 | 42   | 110 | 100 |
|                             | c  | 106 | 107 | 109/78 | 112/78 | 9   | 10   | 3.5  | 3.6  | 33 | 38  | 25 | 39  | 46 | 117  | 114 |     |
|                             | d  | 119 | 121 | 110/81 | 121/5  | 7.5 | 9.5  | 4.7  | 5    | 39 | 47  | 19 | 18  | 48 | 51   | 135 | 125 |
| MM                          | a  | 90  | 90  | 108/57 | 108/57 | 5   | 5    | 1.7  | 1.1  | 19 | 19  | 44 | 44  | 19 | 19   | 100 | 100 |
|                             | b  | 90  | 98  | 108/57 | 110/58 | 5   | 5    | 1.8  | 2.0  | 20 | 20  | 41 | 38  | 20 | 20   | 107 | 103 |
|                             | c  | 95  | 100 | 116/58 | 103/54 | 5   | 4.5  | 2.1  | 2.1  | 21 | 21  | 31 | 33  | 23 | 20   | 114 | 110 |
|                             | d  | 90  | 118 | 127/59 | 111/59 | 4   | 5    | 2.1  | 2.4  | 23 | 20  | 39 | 32  | 26 | 21   | 126 | 129 |
| AT                          | a  | 89  | 89  | 110/47 | 110/47 | 3   | 5    | 2.1  | 2.1  | 24 | 24  | 31 | 32  | 22 | 22   | 100 | 100 |
|                             | b  | 93  | 98  | 110/47 | 117/54 | 3   | 3    | 2.5  | 2.7  | 27 | 28  | 8  | 26  | 29 | 27   | 107 | 107 |
|                             | c  | 107 | 124 | 126/50 | 97/47  | 3   | 3    | 2.9  | 3.2  | 27 | 26  | 26 | 26  | 28 | 23   | 118 | 132 |
|                             | d  | 120 | 137 | 119/47 | 115/46 | 3   | 3    | 3.2  | 3.5  | 27 | 26  | 27 | 26  | 24 | 24   | 124 | 142 |
| AH                          | a  | 5   | 75  | 120/70 | 120/70 | 8   | 8    | 2.8  | 2.8  | 31 | 37  | 31 | 31  | 43 | 43   | 100 | 100 |
|                             | b  | 16  | 90  | 126/70 | 120/67 | 1   | 8    | 3    | 3.3  | 39 | 37  | 30 | 25  | 47 | 41   | 108 | 119 |
|                             | c  | 84  | 93  | 130/64 | 122/60 | 8   | 7.5  | 3.8  | 3.8  | 44 | 39  | 23 | 23  | 52 | 43   | 119 | 125 |
|                             | d  | 93  | 100 | 138/67 | 124/58 | 7.5 | 7    | 4.4  | 4.5  | 46 | 45  | 20 | 18  | 54 | 49   | 145 | 140 |
| RR                          | a  | 107 | 107 | 94/57  | 94/57  | 8   | 8    | 2.3  | 2.3  | 3  | 23  | 30 | 30  | 22 | 21   | 101 | 100 |
|                             | b  | 107 | 108 | 103/68 | 108/70 | 7.5 | 8    | 2.4  | 2.7  | 24 | 25  | 28 | 28  | 26 | 26   | 100 | 102 |
|                             | c  | 109 | 121 | 111/68 | 121/66 | 7.5 | 7    | 2.6  | 2.8  | 24 | 25  | 29 | 27  | 28 | 28   | 106 | 104 |
|                             | d  | 130 | 136 | 130/77 | 103/57 | 8   | 8    | 3.3  | 3.3  | 25 | 24  | 29 | 27  | 32 | 24   | 123 | 121 |
| MA                          | a  | 77  | 77  | 90/45  | 90/45  | 7.5 | 5    | 1.7  | 1.7  | 2  | 2   | 35 | 35  | 18 | 18   | 100 | 100 |
|                             | b  | 101 | 100 | 101/45 | 85/40  | 7   | 7.5  | 2.1  | 2.2  | 21 | 22  | 31 | 25  | 19 | 17   | 130 | 130 |
|                             | c  | 103 | 122 | 110/45 | 90/40  | 7.5 | 7.5  | 2.3  | 2.4  | 2  | 20  | 29 | 24  | 20 | 16   | 137 | 133 |
|                             | d  | 124 | 130 | 118/45 | 95/40  | 7.5 | 7    | 2.5  | 2.6  | 20 | 20  | 28 | 28  | 19 | 16   | 151 | 145 |
| BH                          | a  | 96  | 105 | 87/54  | 97/57  | 9   | 9    | 1.6  | 1.5  | 17 | 14  | 41 | 45  | 15 | 13   | 112 | 100 |
|                             | b  | 96  | 111 | 84/50  | 104/62 | 9   | 8.5  | 1.3  | 1.2  | 18 | 18  | 36 | 38  | 15 | 19   | 140 | 148 |
|                             | c  | 110 | 116 | 85/53  | 81/41  | 8   | 9    | 1.3  | 1.3  | 23 | 20  | 28 | 25  | 20 | 16   | 168 | 172 |
| AR                          | a  | 90  | 100 | 155/85 | 130/5  | 18  | 18   | 1.64 | 1.2  | 18 | 17  | 66 | 54  | 26 | 23   | 100 | 100 |
|                             | b  | 98  | 115 | 150/80 | 140/75 | 14  | 15   | 1.90 | 2.00 | 19 | 19  | 64 | 44  | 27 | 25   | 110 | 111 |
| AP                          | b  | 106 | 120 | 90/44  | 86/40  | 8   | 6    | 1.2  | 1.5  | 11 | 12  | 49 | 39  | 9  | 10   | 80  | 88  |
|                             | c  | 115 | 128 | 104/43 | 107/43 | 6   | 7    | 1.8  | 2.1  | 15 | 16  | 37 | 31  | 14 | 14   | 120 | 118 |
| JK                          | b  | 7   | 90  | 110/55 | 104/55 |     |      | 3.3  | 3.7  | 45 | 41  | 21 | 19  | 45 | 40   | 97  | 100 |
|                             | c  | 81  | 92  | 106/64 | 106/55 |     |      | 3.7  | 3.9  | 46 | 41  | 21 | 18  | 49 | 40   | 105 | 108 |
| LM                          | b  | 83  | 8   | 130/67 | 109/58 | 8   |      | 2.5  | 2.4  | 30 | 28  | 34 | 31  | 35 | 29   | 113 | 105 |
|                             | c  | 88  | 91  | 130/60 | 120/60 | 7   | 8    | 2.7  | 2.6  | 31 | 29  | 31 | 31  | 36 | 31   | 122 | 117 |
| RMc                         | b  | 96  | 110 | 108/2  | 96/60  | 10  | 10   | 1.4  | 1.6  | 15 | 15  | 60 | 45  | 17 | 15   | 95  | 100 |
|                             | c  | 104 | 118 | 114/0  | 104/62 | 10  | 9.5  | 1.6  | 1.8  | 16 | 15  | 53 | 42  | 19 | 16   | 127 | 130 |

$s = 1.2$  (01)  $b = 2.5$  (02)  $c = 5$  (04)  $d = 10$  (08)  $\mu\text{g}/\text{kg}/\text{min}$  d but m ne (as prenaline)  
HR = heart rate BP = blood pressure IABP = intra-aortic balloon pump

HR = heart rate BP = blood pressure LA = left atrial pressure CI = cardiac index SVI = stroke volume index PRI = peripheral resistance index and SWI = stroke work index TMA = percentage increase in transmembrane pressure D = dobutamine I = isoprenaline

**Drug infusion** The patients fell into two groups (1) those on no inotrope and (2) those patients who prior to the study had been stabilized on isoprenaline

1 Patients on no drugs After confirming that

the patient was in a hemodynamically stable state (relatively constant cardiac output blood pressure left and right atrial pressure and heart rate for 1 hour) dobutamine 125 250 500 and 1000  $\mu\text{g}/\text{Kg}/\text{min}$  or isoprenaline 0.1 0.2 0.4 and 0.8

following cardiac surgery by which changes in blood flow and pressure may be more precisely evaluated

### Subjects and methods

**Patients** Fourteen patients (10 men and four women) whose ages ranged from 21 to 56 years were studied. All had undergone cardiopulmonary bypass surgery (repair of atrial septal defect, aortocoronary saphenous vein bypass grafting, and aortic valve replacement) within the preceding 24 hours. Because of considerable hemodynamic variations in the immediate hours following cardiac surgery, these studies were performed when the patients were hemodynamically stable and in most cases this was between 16 to 22 hours after the cessation of bypass. No patient had any mitral or aortic valve regurgitation.

The nature of the investigation was explained and consent was obtained from the patients before the operation.

All the patients were in sinus rhythm and with only one exception were being ventilated. No other drugs or fluids were given during the investigation.

### Methods

**Aortic flow measurement** The use of the Williams Barefoot extractable aortic flow probe, produced a continuous display of aortic flow trace and its derived parameters.\* This flow probe is placed around the ascending aorta during surgery with its cable being exteriorized through a small incision to the right of the sternum. The probe can be left in place for up to a week and when recording has been completed, by cutting an external snare the probe can be removed by gentle traction causing less discomfort to the patient than removal of a conventional drain. The flow probe is connected to a Carolina 601D gated square wave flowmeter which gives a continuous display of cardiac output.

The hemodynamic findings were obtained with equipment designed specifically for precise circulatory monitoring of the critically ill patient after cardiac surgery. The Williams Barefoot extractable electromagnetic flow probe permits the continuous display of ascending aortic flow in the intensive care unit and has proved of great benefit in the assessment and management of patients after open heart surgery. A more precise assessment of the effects of pharmacological and physical interventions is possible than with the conventional pressure and cardiac output mea-

surements hitherto available. Electromagnetic flow probe cardiac output measurements are more accurate than dilution techniques especially in low output states.\* Values measured with the Williams Barefoot flow probe have been compared with rigid electromagnetic flow probe, indocyanine green dilution cardiac output and thermodilution cardiac output. Good correlation with all methods have been obtained. A further advantage of the technique is that it is possible to derive other indices of aortic flow. Peak aortic flow and maximal acceleration of flow,<sup>14</sup> and left ventricular power<sup>11</sup> have been used as indices of myocardial function, and may be readily obtained using this equipment.

**Other measurements** Left and right atrial pressures and arterial pressure (radial or femoral artery) were measured using Statham 23Pd pressure recorded directly on to a Philips eight channel tape recorder and were analyzed downstream by the St Thomas' postoperative monitoring trolley. This enables a continuous digital or meter display of cardiac output, stroke volume, stroke work, an index of peripheral resistance, arterial pressure, left and right pressure and heart rate.

In five patients a coronary sinus sampling line was left in place following surgery, and coronary sinus and arterial samples were taken and analyzed for lactate, pyruvate and oxygen content.

The hemodynamic variables were calculated from the basic data as follows:

### Cardiac Index (CI)

$$= \text{Cardiac output/body surface area (L/min/M}^2\text{)}$$

### Stroke Volume Index (SVI)

$$= \text{Stroke Volume/body surface area (ml/min/M}^2\text{)}$$

### Stroke Work Index (SWI)

$$= \text{SVI} \times (\text{mean arterial pressure} - \text{right atrial pressure}) \times 0.136 \text{ Gm m/min/M}^2$$

$$\text{Systemic vascular resistance Index (SVRI)} = \frac{(\text{mean arterial pressure} - \text{right atrial pressure})}{\text{Cardiac Index}}$$

$$\text{mm Hg/L/min/M}^2$$

The flow trace was passed through a differentiator and the first differential maximal acceleration of flow was measured. The percentage change was calculated using either the resting or initial stable isoprenaline value as control.

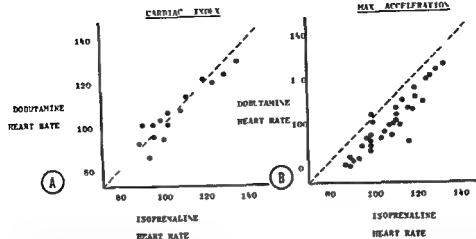


Fig 2 A comparison of the chronotropic effects of isoprenaline and dobutamine. The heart rates produced by both drugs to achieve the same cardiac index (a) and maximal acceleration (b) in the 14 cases studied are plotted

$p < 0.1$  at the highest dose) Both drugs lead to a fall in peripheral resistance but this was more marked with isoprenaline

All patients remained in sinus rhythm during the infusions. In two patients there was a slight increase in ventricular extrasystoles but some ventricular extrasystoles were evident during the control period. The increase was small (two to five ventricular ectopics per minute); no infusion was stopped because of the development of dysrhythmias and there were no changes in ST segments or T waves which were monitored throughout in the investigation.

In the five cases where simultaneous arterial and coronary sinus blood samples were taken there appears to be little difference in the metabolic effects of both drugs (Table II). Compared to control levels there was no difference in A/V oxygen content difference and both drugs appeared to reduce the lactate and pyruvate uptake of the myocardium. There thus appears to be little benefit in myocardial economy from dobutamine when compared with isoprenaline in these patients.

#### Discussion

Currently many drugs are advocated in the treatment of low cardiac output states after cardiac surgery. Dobutamine in the present study has been shown to have an equi potent inotropic effect to isoprenaline with a reduced chronotropic and peripheral vascular action. The changes in maximal acceleration and stroke work at a

constant left atrial pressure occurred at a lower heart rate with dobutamine than with isoprenaline and the drug caused a small elevation in systolic blood pressure. The studies described were performed at a time after surgery when a stable hemodynamic situation had been achieved. This precaution minimizes uncontrollable changes in the circulatory state which often occur in the immediate post bypass period i.e. such variables as fluctuations in the myocardial contractile state, elimination of anesthetic agents, employment of analgesic agents and variable changes in fluid volume. Rastelli and Kirklin<sup>2</sup> have shown depressed cardiac function for 2 to 3 days following cardiac surgery and it seems likely that our results can be extrapolated back to the immediate postoperative period with the advantage that any changes observed in the hemodynamic state were probably induced by the drug.

The cardiovascular effects of dobutamine which have been found in this study are not necessarily beneficial. The cardiac output in patients after cardiac pulmonary bypass would appear to be relatively more dependent on heart rate than stroke volume. Stroke volume is increased only slightly by inotropic agents<sup>11,12</sup> and our results confirm that observation. Since dobutamine has less chronotropic effect than isoprenaline the cardiac output for a given inotropic dose will be less.

The second observed effect of dobutamine was that it provoked a modest elevation of arterial



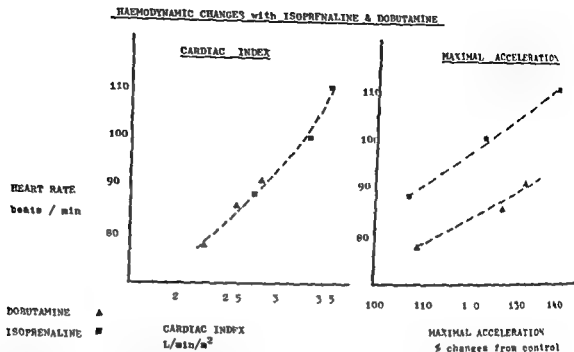


Fig 1 The hemodynamic changes in one patient (H B) during isoprenaline and dobutamine infusions: changes in cardiac index and maximum percentage change from control in acceleration for a given heart rate are compared

$\mu\text{g/Kg/min}$  were given each dose level for 7 to 10 minutes, starting with either drug in a random order with a 1 hour equilibrium interval between the different drug infusions. The dose range was judged from previous reports to be the concentration of the drugs producing identical increments in cardiac output in patients studied during cardiac catheterization.<sup>4</sup>

**2 Patients on isoprenaline** These patients were similarly confirmed to be stable, the isoprenaline dose was then doubled for 10 minutes and was then returned to the control level. Once restabilized the patient was switched to dobutamine at 125 times the dose of isoprenaline for 10 to 20 minutes; the dose was then doubled for 10 minutes. The patient was then placed back onto the initial isoprenaline dose, allowed to stabilize again, the dose was doubled for 10 minutes. Either the isoprenaline data before or after the dobutamine infusion was analyzed, in a random order.

## Results

In both groups of patients in the dose levels chosen, dobutamine appeared to produce an equivalent inotropic effect when compared with isoprenaline. Detailed results of the investigation are given in Table I.

Both drugs produced a dose dependent increase

in myocardial performance as measured by maximum acceleration of aortic flow and stroke work (left atrial pressure changed little during the infusions). Though both drugs caused an increase in heart rate, dobutamine produced its improvement in inotropic action as measured by these two indices at a heart rate 10 to 15 per cent lower than isoprenaline (Figs 1 and 2).

The stroke volume was only slightly altered by increasing doses of both drugs (12.5 per cent and 13.9 per cent increase with the highest doses of dobutamine and isoprenaline respectively). As a result of this, in these patients following open heart surgery, cardiac output is very dependent upon heart rate and thus any difference in chronotropic activity between the two drugs would not be revealed by a measurement of cardiac output alone. Figs 1 and 2 show that the increase in cardiac index with dobutamine and isoprenaline was achieved at almost identical heart rates.

The effects of the drugs upon blood pressure differed considerably. Isoprenaline caused little change in systolic pressure but a fall in diastolic pressure (mean diastolic pressure fall at the highest dose was  $3 \pm 1.5$  mm Hg,  $p < 0.1$ ). In contrast dobutamine maintained diastolic pressure at control levels and there was a moderate rise in systolic pressure ( $15.7 \pm 2.9$  mm Hg).

- name and metabolic responses to vasodilator therapy in acute myocardial infarction *Circulation* 48 1183 19 3
- 4 Jewitt D Burkhead J Mitchell A and Doolery C Clinical cardiovascular pharmacology of dobutamine A selective inotropic catecholamine *Lancet* 2 363 1974
  - 5 Vatner S F McRybae II J and Braunwald E Effects of dobutamine on left ventricular performance coronary dynamics and distribution of cardiac output in conscious dogs *J Clin Invest* 53 196 1974
  - 6 Tuttle H II Pollock G D Todd G and Tust R Dobutamine containment of myocardial infarct size by a new inotropic agent *Circulation* 47(Suppl IV) 139 1973
  - 7 Maroko P R Swain J. and Vatner H Effect of dobutamine on myocardial injury after coronary occlusion *Circulation* 49(Suppl. III) 189 1974
  - 8 Bourne P H and Williams H T A cardiac monitor combining flow and pressure measurement *Biochemical Engineering* 10 453 1975
  - 9 Jacobs R R Heydon W C Williams H T Schmidt U T and Schenk W Z Cardiac output in the exercising dog *J Surg Res* 10 25 19 0
  - 10 Noble M I M Trenchard D and Guz A Left ventricular ejection in conscious dogs, measurement and significance of maximal acceleration of blood from the left ventricle *Circ Res* 19 139 1966
  - 11 Benzing H Stockert J Nave E., Tsuei Y G., and Idaplan S Evaluation of left ventricular contractility *Cardiovasc. Res* 8 313 1974
  - 12 Rastelli G C and Kirklin J W Hemodynamic state early after the replacement of the mitral valve *Circulation* 34 448 1966
  - 13 Jenkins H S Branthwaite M A and Bradley R D Cardiac function after open heart surgery *Cardiovasc Res* 7 297 19 3
  - 14 Holloway H L Schultz C Stinson E and Harrison D C Comparison of circulatory effects of dopamine and isoproterenol immediately following cardiac surgery *Circulation* (Suppl IV)VII and VIII 1/7 1373
  - 15 Cohn J N Blood pressure and cardiac performance *Am J Med* 55 351 1973
  - 16 Sarnoff S J Braunwald E and Welch J R Hemodynamic determinants of oxygen consumption with special reference to the tension time index. *Am J Physiol* 192 148 1968

### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc P O Box 765 Schenectady N Y 12301 518 374-4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale.

Table II Myocardial metabolism during infusions

| Patient initials and drug | Arterial lactate* | % extraction† | Arterial pyruvate | % extraction† | A-V O <sub>2</sub> difference |
|---------------------------|-------------------|---------------|-------------------|---------------|-------------------------------|
| <b>M M</b>                |                   |               |                   |               |                               |
| Control                   | 96                | -23           | 0.109             | -8            | 6.9                           |
| Isoprenaline              | 100               | 0             | 0.105             | 3.8           | 4.2                           |
| Dobutamine                | 108               | 27            | 0.098             | -4.5          | 6.5                           |
| <b>A H</b>                |                   |               |                   |               |                               |
| Control                   | 153               | 11            | 0.153             | 1.1           | 7.2                           |
| Isoprenaline              | 148               | -7.0          | 0.138             | -8.7          | 8.2                           |
| Dobutamine                | 157               | 10.8          | 0.136             | 8.0           | 9.9                           |
| <b>R R</b>                |                   |               |                   |               |                               |
| Control                   | 114               | 14            | 0.159             | 3.0           | 5.2                           |
| Isoprenaline              | 142               | -4.9          | 0.169             | -4.0          | 4.6                           |
| Dobutamine                | 128               | -9.4          | 0.152             | 5.0           | 4.4                           |
| <b>M A</b>                |                   |               |                   |               |                               |
| Control                   | 69                | 10            | 0.092             | 7.6           | 10.3                          |
| Isoprenaline              | 79                | -8.8          | 0.077             | -1.8          | 9.2                           |
| Dobutamine                | 69                | 10            | 0.095             | -3.9          | 7.4                           |
| <b>L M</b>                |                   |               |                   |               |                               |
| Isoprenaline              | 514               | 6.8           | 0.413             | 3.8           |                               |
| Dobutamine                | 517               | -0.9          | 0.413             | -4.6          |                               |

Lactate and pyruvate values are in micromoles/liter

$$\uparrow \text{ extraction} = \frac{\text{coronary sinus conc} - \text{arterial conc}}{\text{arterial conc}} \times 100$$

pressure. In low output states augmentation of aortic flow is more important than maintenance of a high arterial pressure provided that perfusion of vital organs does not fall below a critical value. If the perfusion pressure to the coronary renal and cerebral arteries is adequate then further elevation of arterial pressure may be to the detriment of forward flow from the compromised left ventricle.<sup>15</sup> Pressure work has greater metabolic requirements than volume work.<sup>16</sup> It would appear that elevation of blood pressure is undesirable, especially if brought about by constriction of arterioles in vital organs. Analysis of our measurements in the myocardial A-V differences for oxygen, lactate and pyruvate revealed that similar changes were caused by dobutamine and isoprenaline. The results could be attributed to both an increase in coronary blood flow and substrate utilization by dobutamine or to identical changes in these variables with both drugs.

Dobutamine appears to have little if any advantage over isoprenaline in patients who have

undergone cardiac surgery, but our results should not be interpreted as necessarily applying to other clinical situations in which the cardiac output is reduced, in particular gram negative septicemia and myocardial infarction. There is evidence to suggest that after experimental myocardial infarction in dogs, dobutamine causes less ischemic injury than isoprenaline for the same change in myocardial function.<sup>17</sup> This was attributed to the absence of diastolic hypotension and reduced chronotropic action. The incidence of dysrhythmias was also less than with isoprenaline. Thus in the assessment of the utility or the appropriate use of a particular inotropic agent it may be necessary to define precisely the clinical circumstances.

### Summary

The use of an extractable aortic electromagnetic flow probe to provide a continuous on-line display of ascending aortic flow and cardiac output following open heart surgery is described. Utilizing this equipment, the hemodynamic actions of dobutamine and isoprenaline are compared in 14 patients immediately following cardiac surgery. The study confirmed an inotropic action produced by dobutamine at a heart rate 10 to 15 per cent lower than isoprenaline with less peripheral vascular action. Arterial and coronary sinus blood analyses revealed little difference in the myocardial metabolic actions of either drug. Because inotropic drugs produce only relatively small increases in stroke volume in this group of patients, the rise in cardiac output caused by these agents is more dependent on the effects upon heart rate rather than improved myocardial contractile state and consequently dobutamine has little advantage over isoprenaline in this situation.

We would like to thank Mrs. Fiona Baile for her expert secretarial assistance. We also acknowledge the cooperation of the nursing staff of the intensive care unit at St. Thomas' Hospital and F.H. Lilly Ltd., United Kingdom for financial assistance. Dr. Lewis was supported by the New Zealand National Heart Foundation.

### REFERENCES

1. Wise S D, Gibson D G and Branthwaite M A. Haemodynamic effects of salbutamol in patients needing circulatory support after open heart surgery. *Br Med J* 3:502 1974.
2. Palmer R F and Laxeter A C. Sodium nitroprusside. *N Engl J Med* 292:294 1974.
3. Chatterjee K, Jamnik W, Cruz W, Forrester J, Walensky I, Crutchfield C and Swan H J C. Hemody-

Table I

*Observations from the KCG*

- Duration of left ventricular thrust at  $K_1$  and  $K$
- Duration of isovolumic contraction at  $K_1$  and  $K$

- Duration of ejection retraction at  $K_1$  and  $K$

*Observations from the carotid pulse tracing*

- Shudder waves on the anacrotic hump
- Time to peak percussion wave
- Time to peak tidal wave
- Character of the dirotic notch
- Left ventricular ejection time (LVET)

also had a standard kymetocardiogram (KCG) and carotid pulse tracing recorded within 48 hours of catheterization. The technique of recording the KCG has previously been described.<sup>10</sup> The apparatus consists of a flexible metal bellows suspended from a fixed position over the chest and having on one side a probe with a diameter of 7 mm that is fixed to the precordium in similar positions as the standard leads of an electrocardiogram. The open end of the bellows is connected to a pressure transducer (Statham PL5A) and the absolute chest wall motion as sensed by the bellows during held mid expiration is transmitted to an Electronics for Medicine Recorder (Model DR 8) which gives a graphic record. The resultant trace is the precordial movement usually palpable at the bedside. Records were taken from the positions over the precordium corresponding to the electrocardiographic lead V (K) and V (K'). The carotid pulse tracings were recorded by a glycerin pellet apparatus attached over the carotid artery with impulses transmitted by a transducer (Statham PL5A) and recorded simultaneously with the KCG. Phonocardiograms were obtained with a Cambridge microphone and systolic time intervals measured by computer.

A number of intervals were measured from the kymetocardiogram and carotid pulse tracing. Table I demonstrates these.

A typical recording is shown in Fig. 1.

The intervals are defined as follows. Duration of isovolumic contraction (DURIVC) was measured beginning at 0.04 sec after the onset of the QRS and lasting until the onset of ejection as determined by the onset of carotid upstroke. The duration of left ventricular thrust (DURLVT) was determined by drawing a baseline beginning at 0.04 sec after the onset of the QRS complex and measuring the duration of the intersect

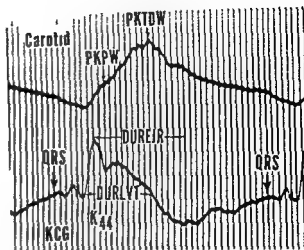


Fig. 1 This figure presents the carotid pulse and the kymetocardiographic tracing from one of the patients with aortic stenosis. The kymetocardiographic record was obtained on the  $K_{44}$  position on the chest wall which is comparable to the electrocardiographic V record but in the fourth intercostal space. The onset of the QRS complexes of the electrocardiogram are indicated by an arrow. The measurements made from these records include the time from the onset of ejection to the peak of the percussion wave (PKPW), the onset of ejection of carotid upstroke to the peak tidal wave (PKTDW), the duration of left ventricular ejection (DURLVT) taken from the kymetocardiographic record (see text) and the duration of ejection retraction (DUREJR). The vertical time lines represent 0.02 sec.

during ejection retraction in the latter phase of systole. The period was measured in hundredths of a second. The duration of ejection retraction (DUREJR) was defined as the interval in hundredths of a second from the peak of forward motion or positive deflection of the kymetocardiogram to the end of systole and beginning of diastolic filling. The ratio of the time intervals of left ventricular thrust to that of isovolumic contraction in the  $K_1$  and  $K'$  positions was utilized in addition to the single measurements. From the simultaneously recorded carotid pulse tracing the time to peak percussion wave (PKPW) and the time to peak tidal wave (PKTDW) were identified as described by Tavel.<sup>10</sup> The initial notching or rounding on the anacrotic hump was judged by visual inspection and defined as the peak percussion wave. This point was occasionally difficult to define but strict criterion adherence allowed consistently reproducible data. The peak tidal wave was defined as the plateau or secondary wave later in systole that occurred immediately prior to the dirotic notch. The ratio of these two values was also considered

# Prediction of aortic valvular area and gradient by noninvasive techniques

A Lucian Cousins, MD  
E E Eddleman, Jr MD  
T Joseph Reeves, MD  
Birmingham Ala

Valvular aortic stenosis is a surgically correctable disease when patient are identified and therapy instituted prior to irreversible decompensation or death. Cardiac catheterization has been extensively utilized to evaluate patients with aortic stenosis and the findings of a peak to peak trans aortic valvular gradient of at least 50 mm Hg and/or a calculated aortic valvular area of 0.8 cm<sup>2</sup> or less have generally been utilized as criteria for surgical intervention. The diagnosis of aortic stenosis and general classification of the severity of the disease in these patients can usually be accomplished by clinical evaluation and bedside examination as has recently been emphasized by Eddleman and associates.<sup>1</sup> Noninvasive diagnostic techniques and/or cardiac catheterization are often necessary to define those patients in need of surgical therapy. The purpose of this paper is to describe a noninvasive system that allows highly significant recognition of the severity of this disease and identification of those in need of valvular replacement.

## Patient selection

Sixty two patients were involved in this study. The criterion for selection was that these patients had cardiac catheterization at the University of Alabama Medical Center Hospital or the

Birmingham Veteran's Administration Hospital. Each patient was found to have isolated aortic valvular stenosis and none had evidence of aortic valvular insufficiency. Those studied were divided into two groups. The initial group consisted of 44 males and six females with an age range of 16 to 77 years and a mean of 51 years. The peak aortic gradient ranged from 12 to 150 mm Hg while the valve area ranged from 0.32 cm<sup>2</sup> to 2.7 cm<sup>2</sup> with the mean for the group 0.96 cm<sup>2</sup>. After the initial patients were evaluated in a retrospective manner to derive formulae by which to calculate aortic valvular area and gradient from noninvasive data, 12 additional patients were studied prospectively to test the formulae as derived. These 12 represent the population available with all necessary data at the time of the study. Ten of these 12 had aortic valvular area calculated and all 12 had peak transaortic valvular gradient measured. Five of the ten patients had a valve area less than 0.8 cm<sup>2</sup> and five had valve area greater than 1 cm<sup>2</sup>. The valve gradients ranged from 20 to 127 mm Hg in these 12 patients varying in age from 21 to 67 years with a mean of 51 years.

These 62 patients represent the total population available with isolated valvular aortic stenosis and complete data as needed for this study at the time of its conduction.

## Measurements and methods

Each patient involved in the study had undergone right retrograde or transseptal left heart catheterization with Fick cardiac output determination and peak transaortic valvular gradient measurement. The valve areas were calculated by the method of Gorlin and Gorlin.<sup>2</sup> Each patient

From the Veterans Administration Hospital and Department of Medicine, University of Alabama in Birmingham School of Medicine, Birmingham, Alabama.

Aided by United States Public Health Services Grant No. HL-11450.

Credit is given to VA Project No. 101-04.

Received for publication Oct. 13, 1976.

Accepted for publication March 1, 1977.

Reprint requests to: A. Lucian Cousins, MD, Georgia Heart Clinic, 109 Medical Drive, La Grange, Ga. 30240.

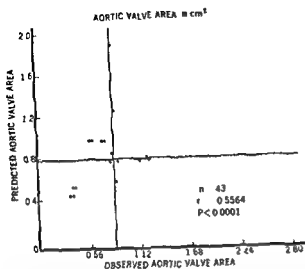


Fig 2 This figure presents the predicted aortic valve area plotted against the observed aortic valve area. The grid has been placed across the record and it can be noted that the 4 patients followed in the left upper quadrant or right lower quadrant were incorrectly identified.

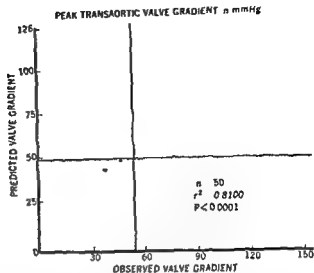


Fig 3 This figure presents the predicted valve gradient versus the observed valve gradient with the grid similarly imposed as in Fig 2. It can be noted that the prediction of the peak transaortic gradient has a greater degree of accuracy than that predicted in the valve area.

gradient by way of noninvasive techniques. Initially, however, the noninvasive and catheterization data were examined together in order to correlate each variable's significance in relation to valve area. Stepwise regression was used in this particular application.

Table II demonstrates that the valve gradient determined from catheterization correlates more closely with the calculated valvular area than any of the variables considered singularly. The individual correlation of the remaining variables is demonstrated in the order of their declining significance.

The same variables were evaluated by the maximum  $r^2$  method to determine the best model for aortic valve area prediction from the noninvasive techniques data. The measured (catheter determined) transaortic valve gradient and calculated valve area were removed from the data prior to this application.

The best of the models for valve area prediction consists of four variables. The  $r^2$  for the four component model is 0.5564 with  $p < 0.0001$ . The variables are as follows: The presence of calcium within the aortic valve (CA), vibration or shudder waves on the anacrotic limb of the carotid tracing (shudder), left ventricular hypertrophy (LVH), and the duration of ejection retraction in the R position (DUREJR R). Table III demonstrates the individual value within the

model as derived and the formula for predicting the valve area as determined by the method.

For numerical purposes the presence of calcium within the valve was assigned the value of 1 if none was present, 0. The duration of ejection retraction was measured in one hundredths of a second and entered as such in the formula. The presence of left ventricular hypertrophy was given the score of 1 if present and 0 if absent, and the presence of shudder waves was given a numerical score of 1 if present and 0 if absent.

Fig 2 is a graphic plot of the predicted area on the vertical axis and the observed area on the horizontal axis for the initial group of fifty patients.

A grid has been superimposed to demonstrate that only eight patients were incorrectly identified as to valve area greater or less than  $0.8 \text{ cm}^2 \pm 1 \text{ cm}^2$ . One was predicted to be less than this limit as measured and seven were predicted to be greater. As illustrated, the  $r$  is 0.5564 and  $p < 0.0001$ . Thirty-five of 43 patients or 82 per cent of the sample were correctly classified as to area of greater or less than  $0.8 \text{ cm}^2 \pm 1 \text{ cm}^2$  by utilizing the derived formula.

The same data were employed to retrospectively predict peak transaortic gradient. Comparison of the 22 variables by stepwise regression reveals that the single most significant variable in

Table II Individual variables and correlation coefficients in aortic valve area prediction

| Variable   | r      | P      |
|--|--------|--------|
| 1 Gradient   | 0.6736 | 0.0001 |
| 2 Calcification of the aortic valve  | 0.5603 | 0.0003 |
| 3 Shudder waves on the anacrotic limb of the carotid pulse tracing                         | 0.4362 | 0.0037 |
| 4 Character of the dirotic wave of the carotid pulse tracing                               | 0.4028 | 0.0074 |
| 5 Left ventricular hypertrophy   | 0.3916 | 0.0092 |
| 6 Age of the patient   | 0.3133 | 0.0385 |
| 7 ST segment depression in Lead V of the ECG   | 0.2389 | 0.1190 |
| 8 Ratio of the duration of LV thrust to isovolumic contraction in $K_1$ of the KCG         | 0.2311 | 0.1372 |
| 9 Time to peak tidal wave from the carotid pulse tracing                                   | 0.2193 | 0.1542 |
| 10 Duration of the isovolumic contraction wave at $K_1$ of the KCG                         | 0.1723 | 0.2685 |
| 11 Ratio of the duration of LV thrust to the isovolumic contraction wave at $K_1$          | 0.1713 | 0.2715 |
| 12 Duration of ejection retraction at $K_1$  | 0.1692 | 0.2839 |
| 13 Duration of LV ejection time from the carotid tracing                                   | 0.1608 | 0.3163 |
| 14 Time to the peak of the percussion wave of the carotid tracing                          | 0.1635 | 0.6793 |
| 15 Duration of the LV thrust at $K_1$ of the KCG   | 0.1449 | 0.6375 |
| 16 Ratio of the duration of the dirotic wave to tidal wave duration of the carotid tracing | 0.1377 | 0.6119 |
| 17 Duration of the isovolumic contractions wave at $K_1$ of the KCG                        | 0.0903 | 0.5764 |
| 18 $\Delta$ LV ejection time from the carotid pulse tracing                                | 0.0804 | 0.6228 |
| 19 Duration of ejection retraction at $K_1$ of the KCG                                     | 0.0730 | 0.6405 |
| 20 Systolic blood pressure   | 0.0641 | 0.7433 |
| 21 Diastolic blood pressure  | 0.3607 | 0.8153 |
| 22 Duration of LV thrust at $K_1$  | 0.0909 | 0.9915 |

as a variable. The dirotic wave or notch was judged independently by at least two observers as being distinct, slurred, or indefinite and given a numerical coefficient for each that is distinct = 1, slurred = 2, and indefinite = 3. The duration of left ventricular ejection time (LVET) was measured from the carotid tracing by computer and compared to that predicted for heart rate ( $\Delta$ LVET) and the presence of vibratory or shudder waves on the anacrotic limb of the carotid tracing was judged by visual inspection. Each patient also had cardiac fluoroscopy

Table III Four component model in aortic valve area prediction

| Variable  | Probability > T |
|---|-----------------|
| Calcium within the valve (CA)   | 0.0009          |
| Shudder waves on the anacrotic (Shudder) limb of the carotid pulse tracing    | 0.0076          |
| Left ventricular hypertrophy (LVH)  | 0.0118          |
| Duration of ejection (DUREJR h)   | 0.1238          |
| Retraction at $K_1$ of the KCG  |                 |
| Formula   |                 |
| Area = 209.22 - (CA) 72.21 - (Shudder) 44.48 - (LVH) 37.23 - (DUREJR h) 31.35 |                 |

performed to determine the presence or absence of calcium in the aortic valve. The brachial blood pressure was measured by pressure cuff. Twelve lead electrocardiograms were evaluated by the criterion of Romhilt and Estes<sup>9</sup> for the presence or absence of left ventricular hypertrophy (LVH). This was entered as a variable as well as ST segment depression or T wave inversion alone in Leads V<sub>1</sub> or V<sub>6</sub>. The age of the patient was also considered as a variable.

### Statistical analysis

Statistical analysis was performed by an IBM 370/155 system using a standard statistical program.<sup>10</sup> This system allowed not only determination of a simple correlation coefficient but additionally, maximum  $r$  improvement analysis. The maximum  $r$  improvement is a technique that approaches an all possible analysis. It begins with the best one variable model with regard to  $r^2$  and then adds the best remaining variables from the multivariate model to consider the effect of switching and finding those available. Once the various combinations have been tried the variables are selected as to which improve the  $r$  the most. The principle distinction between this technique and the stepwise regression is that the latter always removes the least contributor to the prediction and enters the best single variable whereas  $r$  improvement considers all combinations simultaneously. The system yields a formula for determination of the desired value by weighing the contribution of each variable.

### Results

The data were evaluated in order to predict aortic valvular area and peak transaortic valvular

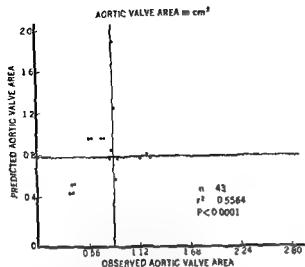


Fig 2 This figure presents the predicted aortic valve area plotted against the observed aortic valve area. The grid has been placed across the record and it can be noted that those patients followed in the left upper quadrant or right lower quadrant were incorrectly identified.

gradient by way of noninvasive techniques. Initially, however, the noninvasive and catheterization data were examined together in order to correlate each variable's significance in relation to valve area. Stepwise regression was used in this particular application.

Table II demonstrates that the valve gradient determined from catheterization correlates more closely with the calculated valvular area than any of the variables considered singularly. The individual correlation of the remaining variables is demonstrated in the order of their declining significance.

The same variables were evaluated by the maximum  $r^2$  method to determine the best model for aortic valve area prediction from the noninvasive techniques data. The measured (catheter determined) transaortic valve gradient and calculated valve area were removed from the data prior to this application.

The best of the models for valve area prediction consists of four variables. The  $r^2$  for the four component model is 0.5564 with  $p < 0.0001$ . The variables are as follows: The presence of calcium within the aortic valve (CA), vibration or shudder waves on the anastotic limb of the carotid tracing (shudder), left ventricular hypertrophy (LVH), and the duration of ejection retraction in the K position (DUREJR K). Table III demonstrates these variables, their individual value within the

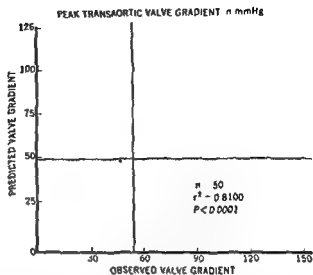


Fig 3 This figure presents the predicted valve gradient versus the observed valve gradient with the grid similarly imposed as in Fig 2. It can be noted that the prediction of the peak transaortic gradient has a greater degree of accuracy than that predicted in the valve area.

model as derived and the formula for predicting the valve area as determined by the method.

For numerical purposes the presence of calcium within the valve was assigned the value of 1 if none was present, 0. The duration of ejection retraction was measured in one hundredths of a second and entered as such in the formula. The presence of left ventricular hypertrophy was given the score of 1 if present and 0 if absent, and the presence of shudder waves was given a numerical score of 1 if present and 0 if absent.

Fig 2 is a graphic plot of the predicted area on the vertical axis and the observed area on the horizontal axis for the initial group of fifty patients.

A grid has been superimposed to demonstrate that only eight patients were incorrectly identified as to valve area greater or less than  $0.8 \text{ cm}^2 \pm 1 \text{ cm}^2$ . One was predicted to be less than this limit as measured and seven were predicted to be greater. As illustrated, the  $r^2$  is 0.5564 and  $p < 0.0001$ . Thirty-five of 43 patients, or 82 percent of the sample, were correctly classified as to area of greater or less than  $0.8 \text{ cm}^2 \pm 1 \text{ cm}^2$  by utilizing the derived formula.

The same data were employed to retrospectively predict peak transaortic gradient. Comparison of the 22 variables by stepwise regression reveals that the single most significant variable in



**Table IV** Individual variables and correlation coefficients in aortic valve gradient prediction

| Variable   | r      | P      |
|--|--------|--------|
| 1 Valve area   | 0.6735 | 0.0001 |
| 2 Time to peak tidal wave  | 0.6549 | 0.0001 |
| 3 Left ventricular hypertrophy   | 0.5502 | 0.0001 |
| 4 Calcification of the aortic valve  | 0.5413 | 0.0002 |
| 5 Shudder waves on the anacrotic limb of the carotid tracing                                     | 0.4755 | 0.0008 |
| 6 Character of the dirotic wave  | 0.4683 | 0.0010 |
| 7 ST wave depression in Lead V <sub>6</sub> of ECG   | 0.3803 | 0.0065 |
| 8 Duration of the ejection retraction in K of KCG  | 0.3722 | 0.0083 |
| 9 Left ventricular ejection time from the carotid pulse tracing                                  | 0.3393 | 0.0174 |
| 10 Δ left ventricular ejection time from the carotid pulse tracing                               | 0.3335 | 0.0194 |
| 11 Time to peak percussion wave of the carotid pulse tracing                                     | 0.2894 | 0.0391 |
| 12 Ratio of dirotic wave to tidal wave duration  | 0.2796 | 0.0614 |
| 13 Ratio of LV thrust to isovolumic contraction wave of K  | 0.2684 | 0.0564 |
| 14 Systolic blood pressure   | 0.2668 | 0.0606 |
| 15 Duration of left ventricular thrust at K of the KCG   | 0.2511 | 0.0751 |
| 16 Diastolic blood pressure  | 0.2314 | 0.1059 |
| 17 Duration of ejection retraction at K of the KCG   | 0.1924 | 0.1822 |
| 18 Age of the patient  | 0.1162 | 0.5729 |
| 19 Duration of LV thrust at the K  | 0.0792 | 0.5948 |
| 20 Duration of the isovolumic contraction wave at K  | 0.0633 | 0.6663 |
| 21 Ratio of duration of LV thrust to duration of the isovolumic contraction wave at K of the KCG | 0.0274 | 0.8461 |
| 22 Duration of the isovolumic contraction wave at K of the KCG                                   | 0.0013 | 0.9894 |

determining the gradient is valve area. When the data from catheterization were removed the single predictors ranked as follows: time to peak tidal wave of the carotid tracing, LVH, the presence of calcium within the valve, shudder waves on the anacrotic limb of the carotid tracing, and in this fashion to the least sensitive predictor: duration of isovolumic contraction at the K<sub>1</sub> position. Table IV lists these individual variables and their respective correlation coefficients for gradient prediction.

Prediction of aortic valvular gradient was performed by a similar procedure to prediction of aortic valve area. A seven variable model gave the most sensitive and applicable determination. The variables included in this are: the presence of

**Table V** Seven component model in aortic valve gradient prediction

| Variable  | Probability > T |
|---|-----------------|
| Left ventricular hypertrophy (LVH)  | 0.0001          |
| Duration of ejection retraction (DUREJR K <sub>1</sub> ) at K of the KCG  | 0.0002          |
| Calcium within the aortic valve (CA)  | 0.0011          |
| Character of the dirotic wave (DICROWAV)  | 0.0011          |
| Left ventricular ejection time (LVET)   | 0.0032          |
| Time to peak percussion wave (TIMPKPW) of the carotid pulse tracing   | 0.0187          |
| Duration of ejection retraction (DUREJR K <sub>1</sub> ) of the KCG   | 0.0335          |
| Formula   |                 |
| $\text{Gradient} = (-79.02) + (\text{CA}) 2.74 + (\text{LVET}) 0.29 + (\text{LVH}) 26.79 + (\text{DUREJR K}_1) 1.61 + (\text{DICROWAV}) 14.99 + (\text{TIMPKPW}) 0.78 - (\text{DUREJR K}_1) 0.75$ |                 |

calcium within the valve (CA), left ventricular hypertrophy (LVH), the duration of ejection retraction in the K<sub>1</sub> position (DUREJR K<sub>1</sub>) the character of the dirotic wave (DICROWAV), the time to peak percussion wave (PKPW), duration of ejection retraction at the K<sub>1</sub> position of the KCG (DUREJR K<sub>1</sub>), and left ventricular ejection time (LVET). Table V lists these variables for gradient prediction and demonstrates the relative significance of each within this particular model. A similar formula to that for valve area determination but applicable to peak transaortic valvular gradient was derived and is demonstrated.

The numerical value for calcium within the valve was the same as previously shown while LVET was measured in msec and was entered as such in formula. The remaining intervals were entered in hundredths of a second.

Fig 3 demonstrates a plot of the predicted gradient along the vertical axis and the observed gradient along the horizontal axis for the initial group.

A grid is again superimposed to correlate the predicted and observed gradient and to define the peak gradient of 50 mm Hg from predicted and observed determinations. This demonstrates that only two patients with a gradient of greater than 50 mm were incorrectly identified and only five were predicted to have a gradient of greater than 50 mm Hg when the observed gradient was less than this significant point. The r for the equation is 0.8100 and p < 0.0001. Forty three of 50

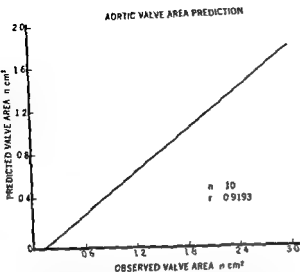


Fig 4 This figure presents a prospective series of patients using the multiple regression equation from the test series. The predicted valve area is plotted against the observed areas. The  $r$  value was 0.9193 and the significance has a  $p < .01$ .

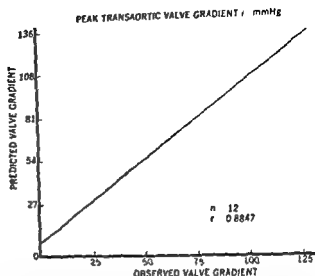


Fig 5 This figure presents the prospective series of patients using the multiple regression equation obtained from the test series. The predicted valve gradient is plotted against the observed valve gradient. The significance of this relationship revealed a  $p < .01$ .

patients or 100 per cent of the sample were correctly classified as to peak gradient of greater or less than 50 mm Hg  $\pm 2$  mm Hg.

The additional 12 patients were then studied in a prospective fashion by these derived formula in order to predict the aortic valvular area and peak transaortic valvular gradient while testing the formulae as derived. Only ten of the 12 patients had aortic valvular area calculated by the method of Gorlin and these are demonstrated in the graph in Fig 4.

All ten patients or 100 per cent of the sample were correctly categorized as to valve area by utilizing the derived formula illustrated in Table III. The correlation coefficient for the prediction is 0.9193.

The peak transaortic valvular gradient predictions were accurate within the group of twelve prospectively tested subjects. These are shown in the graph in Fig 5.

The correlation coefficient of 0.8847 is demonstrated for this evaluation in which ten of 12 patients or 83 per cent of the population were correctly identified by application of the derived formula in Table I.

#### Discussion

Recent advances in aortic valvular surgery have enabled as good as a 90 to 95 per cent five year survival in those undergoing valve replacement.<sup>2,3</sup> Much has been written about impor-

tant signs and symptoms of the disease yet most significant contributions toward descriptors of the process have been cataloged from postmortem data as studies of Wood,<sup>4</sup> Mitchell and colleagues,<sup>5</sup> Grant,<sup>6</sup> Braunwald and Ross,<sup>7</sup> and Morrow and associates.<sup>8</sup> The recent studies of Eddleman and co workers<sup>9</sup> and Bonner and associates<sup>10</sup> have added insight to identification of significant disease in living beings but no prospective study encompassing only objectively obtained data has been reported prior to this writing. This report demonstrates the validity of certain recognized associations and negates others in hemodynamically defined isolated aortic stenosis by examining these singularly and in combination. It should be noted that these findings in all likelihood do not apply to infants and children with aortic stenosis.

Aortic valve area is a sensitive and specific indicator of obstruction to left ventricular outflow. Wood<sup>4</sup> required an area of 75  $\text{cm}^2$  or less before accepting the definition of significant stenosis. The study of Frank and Ross<sup>7</sup> again illustrated the relationship of limited orifice size (70  $\text{cm}^2$ ) and a peak transvalvular pressure gradient of 50 mm Hg as criteria for significant obstruction in that 83 per cent of their patients with that degree of stenosis and without surgery died within a five year follow up period.<sup>11</sup>

Aortic valvular calcification as detected by either chest x ray, cardiac fluoroscopy, or direct

examination is a common finding in severe valvular aortic obstruction. Grant<sup>15</sup> discovered calcification in 65 per cent of stenosed aortic valves. Wood<sup>13</sup> found it in 62 per cent of stenosed aortic valves. Mitchell and associates<sup>14</sup> disclosed it in 80 per cent while Gancey and co workers<sup>20</sup> showed that 90 per cent of patients with aortic stenosis in their study had valve calcification. The series of Eddleman and colleagues<sup>1</sup> indicated that 93 per cent of those with a gradient greater than 50 mm had calcification of the valve. This study supports these previous observations in that 27 of 29 or 93 per cent of the population with an area of 80 cm<sup>2</sup> or less and 40 of 43 or 93 per cent of those with a gradient of 50 mm or greater had aortic valvular calcification by fluoroscopy examination.

Left ventricular hypertrophy (LVH) as determined by electrocardiographic criterion is a common finding in this disease. Mitchell and associates<sup>14</sup> found that 84 per cent (74 of 121) of the patients in his study had left ventricular hypertrophy and Morrow and co workers<sup>17</sup> reported that 87 per cent of those with significant stenosis had LVH while 77 per cent had ST and T wave abnormalities in Leads V<sub>1</sub> and V<sub>6</sub> alone. The presence of LVH as detected by a point score system was found in 27 of 43 or 63 per cent of those with a 50 mm or greater gradient and in 24 of 29 or 83 per cent of those with an area of 80 cm<sup>2</sup> or less in our population. Eddleman and colleagues<sup>1</sup> used a voltage method alone, however, and found that only 71 per cent of those with a 50 mm or greater gradient had LVH. ST and T wave alterations alone in the precordial leads were not found to be as sensitive in our study as had been previously reported.

Prolonged left ventricular ejection time (LVET) as measured by systolic time intervals was described by Garrard and Weissler<sup>21</sup> as being compatible with aortic stenosis. Bonner Sacks and Tavel<sup>18</sup> confirmed their observations and concluded that the LVET corrected for heart rate of 39 sec or less virtually ruled out significant aortic valvular obstruction while an LVET of 43 sec or greater was highly suggestive of severe stenosis. The prolonged LVET as measured by computer methods was found to be a highly significant contributor to prediction of valvular gradient and area in our investigation by stepwise and multivariate analysis.

Alterations of the anacrotic limb of the carotid artery tracing judged visually, including shudder

waves and a prolonged interval to the peak percussion wave, were also found to be reliable contributors to detection of outflow obstruction. The latter is in variance to an earlier report of Lyle and associates<sup>4</sup> in examination of carotid artery slopes, yet this study considered only the visually determined changes rather than characteristics measured by computer techniques.

As the degree of aortic stenosis becomes more severe, the mechanics of valvular closure become altered. A reduced or absent aortic valvular closure sound is a recognized finding in severe stenosis. We visually judged the aortic notch of the carotid tracing as to whether it was distinctly present, slurred or undefinable and found that there is a highly significant correlation among stenosed valves and abnormal aortic notching in that only one of 43 patients with a gradient of 50 mm or greater and none of those with an aortic valve area of 80 cm<sup>2</sup> or less had what was judged to be a normal aortic notch.

The duration of ejection retraction as measured by the kinetocardiogram may be defined as another indicator of left ventricular ejection duration (Fig 1). Our data exhibits a close correlation of both elevated gradient and reduced valvular area with prolonged ventricular contraction as this was included in predictive formulae for reduced aortic valvular area and elevated transvalvular gradient.

The present investigation encompassed a broad spectrum of noninvasively obtainable data with the purpose in mind of identifying important signs in detection of severe aortic valvular stenosis. The result has been to support some previously recognized positive correlates and to question others such as brachial blood pressure. ST and T wave changes of the electrocardiogram as independent signs alone, duration of measurable left ventricular thrust and the age of the patient. The combined findings of calcification of the aortic valve, left ventricular hypertrophy by point score electrocardiographic criterion, abnormal carotid artery tracings with shudder waves, a poorly defined aortic notch by visual inspection and a prolonged left ventricular ejection may help to identify candidates for aortic valvular replacement.

### Summary

Sixty-two patients with isolated aortic valvular stenosis were analyzed by a series of common noninvasive procedures and by cardiac catheter

zation The data from 50 of these were evaluated in a retrospective fashion by multiple regression methods to determine significant objectively obtained predictors of aortic-left ventricular gradient and valvular area Formulae were derived from these analyses and an additional 12 patients were then studied prospectively to evaluate the validity of the predictive formulae

Forty three of 50 patients (86 per cent) were correctly identified as to a gradient of greater or less than 50 mm Hg in the initial group, and all those in the prospectively studied sample were correctly classified Thirty five of 43 patients (82 per cent) of those with valve area data in the first application were correctly classified as to valve area of greater or less than 0.8 cm<sup>2</sup> and all patients in the prospectively studied group were appropriately identified as to the same area

The combined application of the observations of calcification of the aortic valve shudder waves on the anacrotic limb prolonged time to peak of the percussion wave and alteration of the diastolic notch of the carotid pulse tracing left ventricular hypertrophy by electrocardiogram and the altered duration of ventricular ejection time were reliable predictors of elevated aortic-left ventricular gradient and decreased aortic valvular size

We are grateful to Dr Lloyd Hefner for his wise counsel and to Miss Lucile Romey Mrs Martha Crossman Mrs Etruh Todd Mrs Linda Yeck, and Mrs Donna Fullerton for their secretarial assistance

#### REFERENCES

- Eddleman E E Jr, Frommeyer W B Jr, Lyle D P et al. Critical analysis of clinical factors in estimating severity of aortic valve disease *Am J Cardiol* 31:687 1973
- Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve, other valves and central circulatory shunts *Am HEART J* 41:1 1951
- Eddleman E E Jr, Hefner L, Peeves T J et al. Movement and forces of the human heart I The genesis of the apical impulse *Arch Intern Med* 99:401 1957
- Eddleman E E Jr, Willis K, Reeves T J and Harrison T R The kinetocardiogram I Method of recording precordial movements. *Circulation* 28:29 1963
- Bancroft W H Jr and Eddleman E E Jr Methods and physical characteristics of the kinetocardiographic and apexcardiographic systems for recording low frequency precordial motion *Am HEART J* 73:56 1967
- Lyle D P, Bancroft W H Jr, Tucker M et al. Slopes of the carotid pulse wave in normal subjects aortic valvular disease and hypertrophic subaortic stenosis *Circulation* 43:374 1971
- Swartzell R H, Bancroft W H Jr, Macy J, Jr et al. The on line computer system for determining the systolic time intervals *Comput Biomed Res* 6:465 1973
- Tavel M E Clinical phonocardiography and external pulse recording Chicago 1972 Year Book Medical Publishers pp 43-44
- Romhild D W, and Estes E H Jr A point score system for the ECG diagnosis of left ventricular hypertrophy *Am HEART J* 75:757 1968
- Barr A J and Goodnight J H A user's guide to the statistical analysis system Dept of Statistics North Carolina State University 1972
- Kirklin J W Aortic stenosis Medical Grand Rounds from the University of Alabama Medical Center 5: Med J 65:1181 1972
- Kirklin J W and Pacifico A D Surgery for acquired valvular heart disease *N Engl J Med* 288:133-140 1973
- Wood P Aortic stenosis *Am J Cardiol* 1:553 1958
- Mitchell A M, Sackett C H, Hunzinger W J et al. The clinical features of aortic stenosis *Am HEART J* 48:684 1954
- Grant, R T After histories for ten years of a thousand men suffering from heart disease a study in prognosis *Heart* 16:775 1933
- Braunwald E and Ross J Jr Aortic stenosis *Circulation* 37 (Suppl 3) 61:6, 1968
- Morrow A G, Roberts, W C, Ross J, Jr, et al. NIH Clinical Staff Conference Obstruction to left ventricular outflow *Ann Intern Med* 89:1255-1286 1968
- Bonner A J Jr, Sacks, H N and Tavel, M E Assessing the severity of aortic stenosis by phonocardiography and external carotid pulse recordings *Circulation* 38:247 1973
- Frank S and Ross J Jr The natural history of severe acquired valvular aortic stenosis *Am J Cardiol* 19:178 1967
- Glancey D L, Freed T A, Obrien K P, et al. Calcium in the aortic valve roentgenologic and hemodynamic correlations in 142 patients *Ann Intern Med* 71:245 1969
- Garrard CL Jr and Weissler A M Systolic time intervals in cardiac disease (11) *Mod Concepts Cardiovas Dis* 40:5 1971

# Histopathology of the conducting tissue of the heart in Chagas' myocarditis

Zilton A Andrade MD\*  
Sonia G Andrade MD\*  
George B Oliveira, MD\*\*  
Daniel R Alonso MD\*\*\*

Bahia Brazil and New York N Y

In 1909 Chagas first recognized that arrhythmias are the hallmark of the chronic myocarditis produced by the disease he discovered.<sup>1</sup> Electrocardiographic (ECG) correlations with this chronic myocarditis have subsequently stressed the high incidence of conduction disturbances (up to 87 per cent) with right bundle branch block (RBBB) predominating. RBBB was present in 48.3 per cent of 683 patients studied by Laranja and colleagues<sup>2</sup> in Brazil and in 55.7 per cent of 113 patients studied by Rosenbaum and Alvarez in Argentina.<sup>3</sup> Left anterior fascicular block (LAFB) is present in about the same frequency as RBBB and most often coexists.<sup>3</sup> Other ECG findings include atrioventricular block, premature beats ST and T abnormalities and other less important changes.<sup>4</sup> Left bundle branch block (LBBB) is rare being present in only 2 per cent of the cases reported by Laranja and associates.<sup>2</sup>

Chagas disease is a potentially rich source of electrocardiographic and pathologic correlations due to the presence of characteristic myocardial lesions. In spite of this few serial section studies of the atrioventricular conduction system are available making very sketchy our knowledge of the type and distribution of the lesions responsible for the variety of conduction abnormalities characteristic of the disease. Torres and Duarte<sup>5</sup>

and Andrade and Andrade<sup>6</sup> studied random sections through some portions of the conduction system in Chagas' myocarditis and found both inflammatory and fibrotic changes. Lev and co-workers<sup>7</sup> studied two cases of Wolf Parkinson White syndrome with Chagas' disease. They observed chronic inflammation in the conduction system. In a patient with RBBB they also noted extensive fibrosis of the right bundle branch. Rosenbaum and associates<sup>10</sup> described histologic evidence for interruptive lesions in the RBB and in the anterior division of the LBB. In dogs infected with *T. cruzi* Anselmi and colleagues<sup>11</sup> noted that the delay in AV conduction correlated with fibrotic and inflammatory changes in the AV node and the bundle of His. Oliveira and co-workers<sup>1</sup> described a combination of inflammatory degenerative and fibrotic changes in a series of 30 cases of chronic Chagas' myocarditis.

In this report we describe the pathologic abnormalities of 25 patients with Chagas' myocarditis and correlate them with the electrocardiographic findings. A technique which employs complete serial sections mounted on continuous transparent plastic tape was utilized.

## Materials and methods

Twenty-five patients who died with Chagas' myocarditis in Salvador Bahia Brazil were selected for study. Complete autopsies were performed in all. Both clinical and pathologic features established the diagnosis of Chagas' disease. These features are described in detail elsewhere. Complement fixation tests for *T. cruzi* infection (Guerreiro Machado reaction) and/or xenodiagnosis were positive in all cases. Table I shows the main clinicopathologic and electrocar-

From the Departments of Pathology and Medicine, University of Bahia School of Medicine Salvador Bahia Brazil and the Department of Pathology, Cornell University Medical College New York N Y.

Supported by grant No. SIP/08-083 from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Received for publication Oct. 21, 1976.

Accepted for publication Nov. 2, 1976.

Reprint requests: Zilton A. Andrade, Rua Padre Feijó 31, Anexo I da Faculdade de Medicina, 4000 Salvador, Bahia, Brazil.

Table 1 General data on 25 cases of Chagas heart disease selected for clinicopathological study of the conducting system

| Main ECG findings        | No of cases | Sex |   | Age (yrs) |      |     | Heart weight (Gm) |      |     |
|--------------------------|-------------|-----|---|-----------|------|-----|-------------------|------|-----|
|                          |             | M   | F | Min       | Aver | Max | Min               | Aver | Max |
| RBBB + LAFB              | 15          | 9   | 6 | 21        | 38   | 64  | 220               | 572  | 800 |
| RBBB + LPFB              | 7           | 0   | ~ | 20        | —    | 44  | 450               | —    | 670 |
| LBBB                     | 2           | 2   | ~ | 43        | —    | 58  | 600               | —    | 670 |
| Complete A V block       | 5           | 3   | 2 | 32        | 50   | 73  | 450               | 550  | 800 |
| Absence of cardiac block | 1           | 1   | ~ | —         | 17   | —   | —                 | 410  | —   |

Acute Chagas disease

Not Chronic diffuse myocarditis with interstitial fibrosis was present in all cases and its degree varied from moderate (++) to marked (+++)

diographic findings of the cases studied. The ECG tracings were analyzed according to the criteria of the New York Heart Association.<sup>11</sup>

One patient, case No. 1 died during the acute phase of Chagas disease. He presented with a three week history of unilateral palpebral edema (Romana's sign) and fever. *T. cruzi* were found in preparations from peripheral blood. He was living in an endemic area for Chagas disease and had a positive Guerreiro Machado reaction several months antemortem. Whether he had a relapse or a reinfection resulting in the acute disease is not known. All the other patients (cases No. 2 to 25) had chronic Chagas myocarditis and died with progressive heart failure. In no case was there clinical or pathologic evidence of any other form of heart disease.

The hearts were opened in the usual manner and were fixed in 10 per cent formalin for three or four days. A block was cut from base of the atrial septum and upper third of the ventricular septum according to the methods described by Lev and associates<sup>12</sup> for the study of the AV conducting system. The block was divided in two or three parts embedded in paraffin and cut serially. All sections (5 microns in thickness) were mounted on a continuous 35 or 70 mm plastic tape according to the method described by Pickett and Sommer.<sup>13</sup> Approximately two to six thousand sections were obtained from each block containing the AV conduction system. Sections were stained by the Masson's trichrome method. Available for study in all cases were the AV node, His bundle and proximal portions of the bundle branches and Purkinje's fibers. The sinus atrial node (SAN) was studied in 12 cases, following Hudson's<sup>14</sup> technique but with serial sections being mounted on transparent plastic tape.

Representative sections taken from several

areas of both atria and ventricles were also studied by conventional histologic methods.

Multiple random sections taken from posterior atrial walls (areas around the entrance of the inferior vena cava and in between the pulmonary veins) were utilized for the study of the intracardiac autonomous nervous ganglia.

## Results

**Acute Chagas myocarditis.** Case 1. The pathologic findings were characterized by inflammatory changes throughout the conducting system. The conducting fibers were separated by a moderate degree of edema and diffuse mononuclear infiltrates. Histocytes, lymphocytes and plasma cells constituted the main inflammatory cells but small foci of polymorphonuclear infiltrates were also observed. Amastigote forms (multiplying forms of *T. cruzi*) were scattered throughout the AV conduction system. Vascular congestion was prominent. No necrosis, hemorrhage, calcification or fibrosis was seen. Ruptured amastigote containing myofibers were surrounded by inflammatory cells. Similar but more severe changes were seen in the contractile myocardium.

The ECG showed low voltage and ST and T abnormalities (Fig. 1). There were atrial fibrillation with a high ventricular response.

**Chronic Chagas myocarditis with RBBB and left anterior fascicular block.** Fifteen cases can be described together because they all present essentially similar histopathologic findings. The ECG abnormalities were also essentially the same (Fig. 2). The different areas of the AV conduction system showed varying degrees of involvement and will be described separately.

**AV node.** Examination revealed a mild diffuse fibrosis with scattered foci of lymphocytes

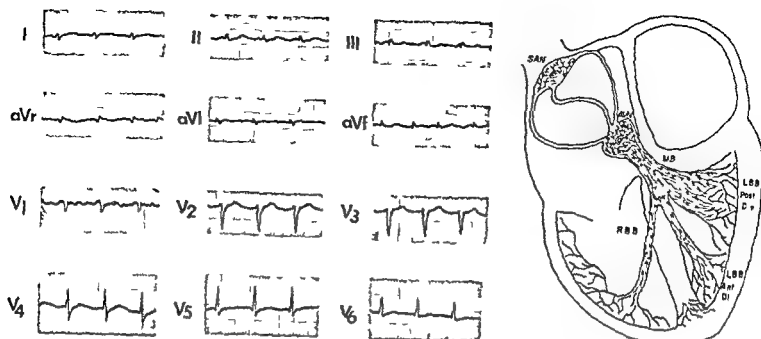


Fig 1 Seventeen year old male patient Three week illness Atrial fibrillation with high ventricular response

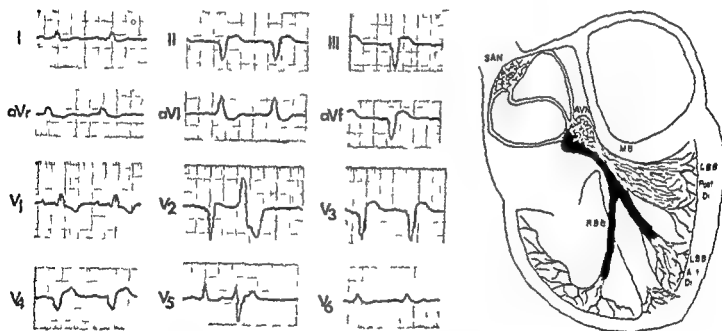


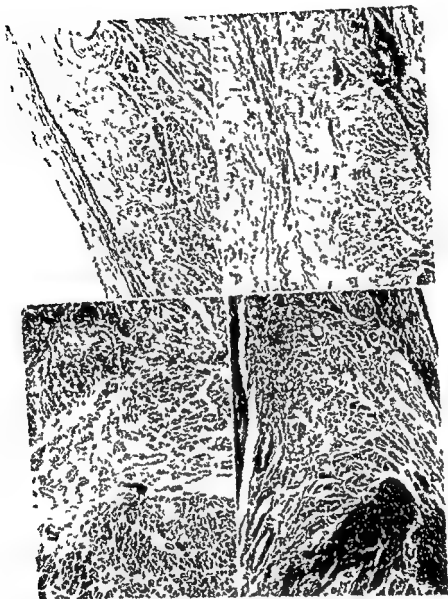
Fig 2 Twenty nine year old male patient Seven month illness Right bundle branch block and left anterior fascicular block

macrophages and a few plasma cells. At the inferior (distal) portion of the node there were areas of fibrosis, muscular atrophy, and fatty infiltration. These areas became more apparent in the penetrating portion. In two cases the nodal artery showed intimal thickening as well as fibrosis and hyalinization of the media.

**His bundle.** Selective involvement of the right half of the His bundle was a striking feature in these cases (Fig 3). The left half showed minimal or no abnormalities. Pathologic changes in the right half of the His bundle consisted of diffuse

fibrosis, focal lymphocytic infiltration, muscular atrophy, and mild fatty infiltration. In addition, there were vascular abnormalities characterized by tortuous, dilated, sclerosed, thick-walled channels with a few atrophic myocardial fibers among them. Often these abnormal vessels were more numerous in the right side of the His bundle and partially replaced it. Occasionally these abnormal vessels were seen in the left half of the His bundle, particularly in the region of the bifurcation.

**Left bundle branch.** The proximal 2.5 to 3 cm



**Fig. 3** Four examples of the selective lesions affecting the right half of His bundle. *Upper right* the penetrating portion of the His bundle already shows fibrosis and myofiber atrophy at the right half. *Upper left* while the left portion of the His bundle is preserved there is fibrosis, atrophy and chronic inflammation involving the right half. *Bottom right* a comparison can be made between the normal looking left half of the His bundle and its diffusely fibrotic right half. *Bottom left* the lesions affecting the right half of the His bundle in this case are represented by vascular dilatation, fatty infiltration, atrophy of specific fibers and lymphocytic infiltration.

of the left bundle was examined. Focal lesions consisting mainly of fibrous replacement of myofibers were seen throughout the left bundle. The anterior division was more severely involved. In addition to fibrosis, there were focal changes similar to those described above, namely, atrophy of myofibers, chronic inflammation and small vessel changes.

**Right bundle branch.** Moderate to severe involvement of the right bundle branch was

present in all 15 hearts. The changes were of a focal or segmental nature and were characterized primarily by fibrosis and atrophy and/or necrosis of conducting myofibers. The vascular changes noted in the His bundle occasionally extended toward the proximal portions of the right bundle. A few lymphocytes were scattered in between the fibers of the right bundle branch.

**Purkinje fibers.** The subendocardial Purkinje fibers were usually normal. Rare foci of subendo-



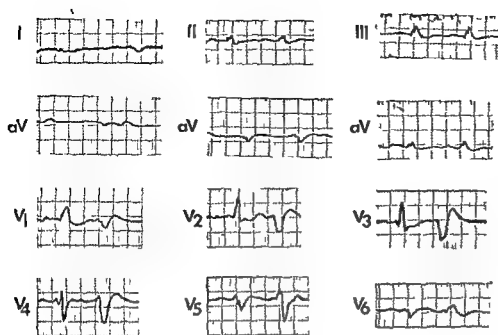


Fig 4 Forty one year old male patient Six month illness Right bundle branch block and left posterior fascicular block

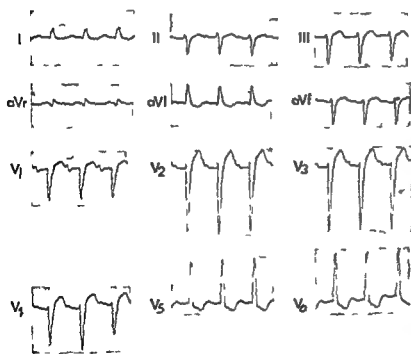


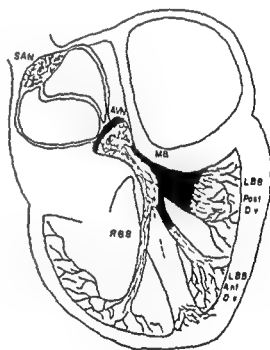
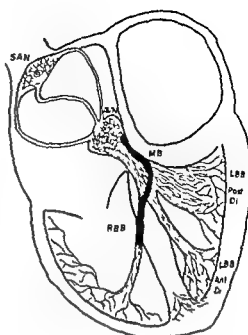
Fig 5 Fifty eight year old male patient Three year illness Complete left bundle branch block

cardial fibrosis occasionally replaced Purkinje fibers in the distal portions of the left bundle branch

**Chronic Chagas myocarditis with RBBB and LPFB** This pattern is exemplified by two cases in which there were moderate to severe fibrosis atrophy and vascular changes in the His bundle RBB and posterior division of the left bundle with total preservation of the anterior division (Fig 4)

**Chronic Chagas myocarditis with complete**

**LBBB** Two cases had this electrocardiographic pattern In one case serial sections showed diffuse fibrosis extending from the AV node to the bundle branches with no selective involvement of the right half of the His bundle The short His bundle bifurcated early The left bundle branch was a distinct tract that came off the His bundle as a compact fascicle This is in contrast with the usual pattern in which fibers originate from the His bundle a few at a time over a considerable area This compact left bundle was completely



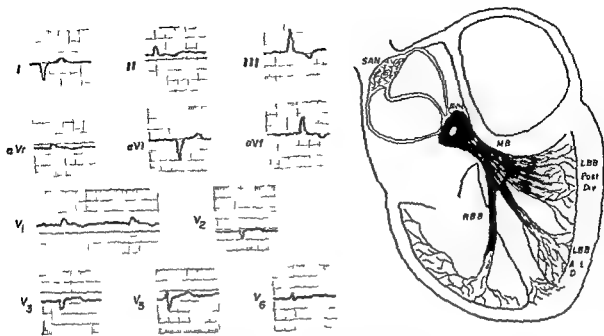


Fig 6 Forty-one year-old female patient Ten month illness Complete atrioventricular block.

interrupted by dense fibrosis and focal calcification in the proximity of the summit of the intraventricular septum. The entire AV conduction system in this case showed very marked vascular changes consisting of tortuous channels with thickened and hyalinized walls and focal luminal stenosis. The right bundle branch showed moderate focal fibrosis and atrophy with rare foci of chronic inflammation. In the other case a diffuse atrophy was present in the entire LBB while the other parts of the AV system were preserved except for the anterior half portion of the AV node which was replaced by fibrosis (Fig 5).

**Chronic Chagas myocarditis with complete (third degree) AV block.** Five cases showed this ECG change. Lesions of fibrosis, atrophy, fatty infiltration, vascular dilatation and thickening were diffusely distributed throughout the AV conduction system (Fig 6). In two cases the AV node, the main bundle, and the right bundle branch were more severely affected. In one case the main lesions were localized in the distal portions of the bundle branches and consisted of sclerosis and atrophy.

**S4 node.** Moderate to marked fibrous replacement of the specialized muscle fibers occurred in all cases, together with a slight to moderate degree of infiltration by lymphocytes, plasma cells and macrophages. Sinus artery showed

hypertrophy of the media and subendothelial fibrous thickening. In one case this latter change was an outstanding one (Fig 7).

**Intracardiac autonomic nervous ganglia.** Changes were present in all 12 cases studied. The ganglia showed a considerable decrease in the number of nerve cells which appeared replaced by fibrosis and proliferation of per ganglionic cells (satellitosis). Infiltration by mononuclear inflammatory cells occurred within and around the ganglia.

No difference could be detected in the nature and degree of changes present in the ganglia taken from the right as compared to those from the left atrial wall.

Purkinje fibers were frequently damaged by acute and chronic inflammation and fibrosis as were ordinary myocardial fibers.

## Discussion

Rosenbaum and associates<sup>1</sup> suggest on the bases of their and other investigators observations that the high incidence of RBBB and LAFB in chronic Chagas myocarditis is to be predicted in a panmyocarditis. The right bundle branch is longer than and follows an intramyocardial course while the left bundle branch is shorter, spreads over a large area and is primarily subendocardial. Therefore Rosenbaum and associates predict that the evenly distributed random



**Fig 7** Upper right SA node showing considerable thickening of the nodal artery, atrophy of fibers, chronic inflammation and fatty change. This patient presented sinus dysfunction and sudden death. Upper left a subendocardial portion of the right bundle branch disclosing fibrosis and small vessel changes. Bottom right considerable vascular ectasia is seen in the vicinity of the AV node. These vascular alterations usually would proceed along to the His bundle and its branches. Bottom left diffuse sclerosis, vascular dilatation, inflammation, atrophy, and fragmentation of specific muscular fibers can be observed in the His bundle and its branches. From a case of complete AV block.

lesions of a panmyocarditis would most likely cause interruption of the right bundle branch most often the left anterior division next in frequency and the left posterior division least often.

Our findings demonstrate that the lesions of chronic Chagas myocarditis are not distributed randomly through the atrioventricular conduction system. In the cases of chronic Chagas myocarditis that we have studied there is clearly a preferential distribution of the lesions within the conduction system. The electrocardiographic findings reflect this distribution.

In case No. 11 with RBBB and LAFB there are

only minimal inflammatory changes in the right bundle while the right side of the His bundle, the AV node and the anterior division of the left bundle are the sites of fibrosis, necrosis and atrophy of the conduction fibers. This suggests that the disruption of the conduction to the RBB is occurring at some point proximal to it and supports the Sherf and James' hypothesis<sup>11</sup> that longitudinal dissociation occurs within the fibers of the His bundle. The inflammatory changes observed in the right bundle branch are unlikely to account for the RBBB pattern since it is known that RBBB does not occur in the acute states of Chagas myocarditis when the inflam-

matory lesions predominate.<sup>2</sup> In our own case No 1 of severe acute Chagas myocarditis which resulted in death of the patient conduction disturbances were absent in spite of massive inflammation and presence of intracellular parasites.

This study offers an alternate explanation to the conduction disturbances characteristic of chronic Chagas myocarditis. Careful examination of thousands of histologic serial sections of the atrioventricular conduction system unexpectedly revealed small focal strategically located lesions involving predominantly the right half of the His bundle, the right bundle and the anterior division of the left bundle branch. This distribution closely follows the known electrocardiographic evidence of conduction disturbances. Selective involvement of the right half of the His bundle has been considered as a cause of RBBB by Corsi and colleagues<sup>3</sup> and this suggestion has been experimentally supported. Such selective lesion has also been noted by Lev and co-workers<sup>4</sup> in three cases of idiopathic myocarditis and by Oliveira and associates<sup>5</sup> in chronic Chagas myocarditis.

In particular the peculiar localization of the lesion to the right half of the His bundle was most striking. Why should an inflammatory or degenerative lesion remain limited to one side of the His bundle? There does not seem to be any significant difference in the distribution of blood vessels, lymphatics<sup>6</sup> or nerves.<sup>7</sup>

Changes in the intracardiac autonomic nervous system were present in all cases examined. They did not correlate either in degree or location with the changes present in the conduction system. However much remains to be learned about the relationships of the conduction system and the autonomic innervation of the heart.

Lesions affecting the conduction system in chronic Chagas myocarditis are progressive. Cases presenting with complete AV block show an end stage picture with diffuse fibrosis, fatty infiltration and inflammation that differ from the simple sclero atrophy of distal branches described in cases not associated with Chagas disease.<sup>8</sup>

Pathogenesis of the lesions found in the conducting system is rather difficult to explain. Pathogenesis of Chagas myocarditis itself is still obscure.

The polymorphism and variable combinations of the lesions are suggestive of a complex and

multifactorial pathogenesis. The basic lesion is inflammation. However vascular and nervous factors probably play a role. More data on the role of lymphatics and the autonomic nervous system of the heart seem necessary for the understanding of the pathogenesis of the changes affecting the conducting tissue of the heart in chronic Chagas myocarditis.

### Summary

The conducting tissue of the heart was studied in 25 human cases of Chagas myocarditis with a method which employs complete serial sections mounted on continuous transparent plastic tape. The pathological changes were correlated with electrocardiographic findings.

The inflammation of the acute phase of Chagas myocarditis as seen in one single case did not seem to interfere with conduction through the AV system.

In chronic Chagas myocarditis the conducting tissue showed extensive and variable changes: chronic inflammation, fibrosis, atrophy and fragmentation of specific fibers, extreme dilatation and tortuosity of veins, capillaries and lymphatics, fatty infiltration and arterial medial and intimal fibrosis.

A preferential involvement of the right bundle branch and the anterior fascicles of the left branch was observed and an excellent correlation with electrocardiographic abnormalities was found. There was also evidence presented that bundle branch block may be caused by disease proximal to the bundle branches.

Complete AV block seemed to be the final result of the progressive inflammatory and degenerative changes involving the conduction system in chronic Chagas myocarditis.

Inflammation and fibrosis did also involve the sinoatrial node, Purkinje fibers, intracardiac nervous ganglia and the contractile myocardium.

### REFERENCES

1. Chagas C. Processos patogênicos da tripanosomíase americana. Mem Inst Oswaldo Cruz 11: 5, 1916.
2. Rosenbaum M B. Chagasic myocardiopathy. Progr Cardiovasc Dis 3: 199, 1964.
3. Laranjeira F S, Dias E, Nobrega G and Miranda A. A clinical epidemiologic and pathologic study. Circulation 14: 1035, 1956.
4. Rosenbaum M B and Alvarez A J. The electrocardiogram in chronic chagasic myocarditis. AM HEART J 50: 497, 1955.

- 5 Rodrigues N Os hemibloqueios na miocardiite chagásica. Estudo eletrocardiográfico e vectocardiográfico de 300 casos. *Arq Bras Cardiol* 25 (Suppl 1) 103 1972
- 6 Drs J C P and Kloetzel K The prognostic value of the electrocardiographic features of chronic Chagas disease. *Rev Inst Med Trop S Paulo* 10 158 1968
- 7 Torres C M and Duarte E Lesões do feixe de His-Tawara na cardiomyite chagásica aguda e crônica. Primer Reunión Panamericana sobre Enfermedad de Chagas 1 23 1950
- 8 Andrade Z A and Andrade S G A Patologia da doença de Chagas (Forma Crônica Cardíaca). *Bol Fund Gonçalo Moniz* 6 1 1955
- 9 Lev M Kennamer R Prinzmetal M and Mesquita Q H A histopathologic study of the atrio-ventricular communications in two hearts with the Wolff Parkinson White Syndrome. *Circulation* 24 41 1961
- 10 Rosenbaum M Lazzari J O Kreis A and Ruos H O The clinical causes and mechanisms of intraventricular conduction disturbances. In: *Advances in electrocardiography* Schlant R C and Hurst J W editors. New York 1972 Grune & Strat on Inc
- 11 Anselmi A Gurdil O Suarez J A and Anselmi G Disturbances in the A V conduction system in Chagas myocarditis in the dog. *Circ Res* 20 56 1967
- 12 Oliveira J A M Oliveira J S M and Koberle F Pathologic anatomy of the His-Tawara system and electrocardiographic abnormalities in chronic Chagas heart disease. *Arq Bras Cardiol* 25 17 1972
- 13 *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. Boston 1973 New York Heart Association Little Brown & Company
- 14 Lev M Widran J and Erikson M A method for the histopathologic study of the atrio-ventricular node bundle and branches. *Arch Pathol* 52 73 1951
- 15 Pickett H T P and Sommer J R Thirty five mm film as mounting base and plastic spray as cover glass for histologic sections. *Arch Pathol* 69 239 1960
- 16 Hudson R E B *Cardiovascular Pathology* Vol 1 Chapter 2 The conducting system pp 53 145 London 1960 E Arnold Publishers Ltd
- 17 Sherf L and James T N A new electrocardiographic concept Synchronized sino-ventricular conduction. *Chest* 55 127 1969
- 18 Corsi V Sciacca A Sangiorgi M and Farulla A Etude histologique pour coupes sèches du faisceau de Paladino His dans un cas de bloc de branche du type rétrograde. *Acta Cardiol* 8 409 1953
- 19 Sciacca A and Sangiorgi M Trouble de la conduction intraventriculaire droite du a la lésion du tronc commun du faisceau de His (Etude expérimentale). *Acta Cardiol* 12 486 1957
- 20 Lev M Unger P N Lesser M F and Pick A Pathology of the conduction system in acquired heart disease. Complete right bundle branch block. *Am Heart J* 61 593 1961
- 21 Frank R J and James T N Normal blood supply to the human His bundle and proximal bundle branches. *Circulation* 47 8 1973
- 22 Symbas P N Cooper F Gantner G F and Willman V L Lymphatics of the heart. *Arch Pathol* 81 1 1966
- 23 Titus J L Anatomy of the conduction system. *Circulation* 47 170 1973
- 24 Lenegre J Etiology and pathology of bilateral bundle branch block in relation to complete heart block. *Progr Cardiovasc Dis* 6 409 1964
- 25 Davies M J A histological study of the conduction system in complete heart block. *J Pathol Bact* 94 351 1967
- 26 Andrade Z A and Andrade S C Chagas disease (American trypanosomiasis) in Marcial Rojas. *Pathology of protozoal and helminthic diseases* Chapter 9 Baltimore 1971 The Williams & Wilkins Company

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

## Total effective compliance of the vascular bed in essential hypertension

G M London MD  
M E Safar MD  
Y A Weiss MD  
Ch A Simon MD  
Paris France

Capacitance vessels which affect the filling of the heart may play an important role in the control of cardiac output of hypertensive patients. Most of the previous studies in hypertension were based on the estimation of pressure-volume relationships in segments of cutaneous veins and/or forearm vascular beds.<sup>1</sup> However a quantitative evaluation of the role of capacitance vessels requires the determination of the overall pressure-volume relationship of the total systemic venous bed. In animals such a determination is easy to obtain when the heart is stopped. In humans a similar relationship between total blood volume and central venous pressure can be established when the heart is beating.<sup>2-4</sup> In such a determination the elastic properties of the vascular bed cannot entirely explain the pressure changes in the central veins. Secondary effects of blood volume changes on arterial hemodynamics and venous tone also contribute to variations in central venous pressure. In this case the term effective compliance is used to describe the correlation

The purpose of the present study is to determine total effective compliance in permanent essential hypertensive patients and to evaluate the role of capacitance changes in the control of cardiac output in these subjects

### Material and methods

**Patients** The study was performed in 31 men: nine normotensive controls and 22 permanent essential hypertensive patients. Permanent hypertensive patients were untreated or had discontinued their therapy at least 4 weeks before the study. They were hospitalized for 6 days and placed on a diet containing 110 mEq sodium per day. On the third day of hospitalization diastolic pressure was constantly equal to or above 90 mm Hg.

Extensive investigations included blood and urinary electrolytes, catecholamine determinations, endogenous creatinine clearance, and timed intravenous urography. All patients were listed as essential hypertensives. Clinical characteristics are indicated in Table I. Mild to moderate left ventricular hypertrophy was observed in eight patients. None had cardiac or neurologic involvement.

The protocols were approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Consent for investigations was obtained from the patients after a detailed description of the procedure.

**Hemodynamic parameters** On the third day of hospitalization hemodynamic studies were per-

The work was performed by the Hemodynamic Laboratory of the Hypertension Research Center (Pr. Ag. SAFAR) Department of Prof. M. U. Broussais Hospital, Paris France.

This study was supported by a grant-in-aid from the Institut de la Santé et de la Recherche Médicale (INSERM Paris) the Association pour l'Utilisation du Revenu Artistique (AURA Paris) and the Délégation Générale à la Recherche Scientifique et Technique (DGRST).

Received for publication June 13, 1977

Accepted for publication May 11, 1977

Reprints requested: Pr. Ag. M. Safar, Hôpital Broussais, 96 rue D. D. 75014 Paris, France.

Table I Clinical characteristics

|                                     | Controls    | Hypertensives |
|-------------------------------------|-------------|---------------|
| Number of patients                  | 11          | 22            |
| Age (years)                         | 33 ± 4      | 37 ± 2        |
| Weight (kg)                         | 66 ± 4      | 76 ± 3†       |
| Height (cm)                         | 173 ± 2     | 175 ± 1       |
| Body surface area (M <sup>2</sup> ) | 1.78 ± 0.05 | 1.90 ± 0.03** |

± 1 standard error of the mean

p value &lt; 0.01

†p value &lt; 0.05

Table II Hemodynamic parameters

|                             | Controls   | Hypertensives |
|-----------------------------|------------|---------------|
| Number of patients          | 9          | 22            |
| SAP (mm Hg)                 | 129 ± 3    | 184 ± 5       |
| DAP (mm Hg)                 | 76 ± 2     | 106 ± 3 *     |
| MAP (mm Hg)                 | 97 ± 2     | 134 ± 4 *     |
| CVP (mm Hg)                 | 42 ± 0.8   | 57 ± 0.4      |
| CI (ml/min/M <sup>2</sup> ) | 3747 ± 196 | 3356 ± 84     |
| SI (ml/M <sup>2</sup> )     | 51 ± 4     | 45 ± 3        |
| HR (beats/sec)              | 76 ± 4     | 77 ± 2        |
| TPR (dyne sec cm/M)         | 2110 ± 136 | 3170 ± 112**  |
| TBV (ml/M)                  | 2978 ± 118 | 2711 ± 50     |
| TPV (ml/M)                  | 1650 ± 57  | 1483 ± 33 *   |
| CPBV (ml/M)                 | 711 ± 36   | 667 ± 26      |
| CPBV/TBV (%)                | 24.1 ± 1.3 | 24.4 ± 0.8    |

± 1 standard error of the mean

p value &lt; 0.05

p value &lt; 0.01

p value &lt; 0.001

Abbreviations: SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; CVP = central venous pressure; CI = cardiac index; SI = stroke index; HR = heart rate; TPR = total peripheral resistance; TBV = total blood volume; TPV = total plasma volume; CPBV = cardiopulmonary blood volume.

formed after the patients had fasted overnight. No premedication was administered. Under local procaine anesthesia an antecubital vein and brachial artery were catheterized and the catheters were advanced into the right atrium and the aortic root immediately distal to the aortic valves respectively. Central venous pressure was measured with a Statham strain gauge. An imaginary line parallel to the experimental table and at one third of the distance between the anterior chest wall and the table was used as baseline for the gauge. A large forearm vein was cannulated for infusion. With the subject in the supine position cardiac output was measured at least

Table III Correlation coefficients of the relationships between effective vascular compliance and other clinical and hemodynamic variables in hypertensive patients

| Correlation of effective compliance with | r value† |
|--|----------|
| Age                                      | -0.33    |
| Weight                                   | -0.10    |
| Height                                   | -0.14    |
| BSA                                      | -0.15    |
| SAP†                                     | -0.57    |
| DAP                                      | -0.58 *  |
| MAP                                      | -0.62    |
| CVP                                      | -0.23    |
| CI                                       | -0.58    |
| SI                                       | -0.32    |
| TPR                                      | -0.21    |
| CPBV                                     | -0.45    |
| TBV                                      | 0.03     |
| CPBV/TBV                                 | -0.58    |

p value &lt; 0.05

p value &lt; 0.01

†No correlation coefficient was significant in control subjects

‡See Table II for abbreviations

three times using Waters Cuvette and densitometer as previously described.<sup>9,10</sup> Indocyanine green (5 mg) was introduced into the central venous catheter and flushed into the circulation in less than 0.5 sec. With a constant rate pump blood was withdrawn from the arterial catheter through the densitometer. Blood was reinfused. The system was calibrated before each determination. Curves were measured planimetrically. Cardiac output was expressed in ml/min/M<sup>2</sup>, thus correcting for body surface area. Arterial pressure and central venous pressure were measured with a Siemens recorder. Total peripheral resistance (TPR) was calculated according to the formula

$$TPR = \frac{MAP}{CI} \times 80$$

(dynes sec cm<sup>-1</sup>/M<sup>2</sup>)

where MAP was mean arterial pressure (mm Hg) and CI was cardiac index (ml/min/M<sup>2</sup>).

Cardiopulmonary blood volume was defined as the volume between the right atrium and the tip of the arterial catheter. It was calculated by the Stewart-Hamilton method as follows:  $CPBV$  (ml/M) =  $CI$  (ml/min/M<sup>2</sup>) ×  $MTT$ , where  $MTT$  is the mean transit time in seconds from the right atrium to the tip of the arterial catheter. The correction for the sampling system was

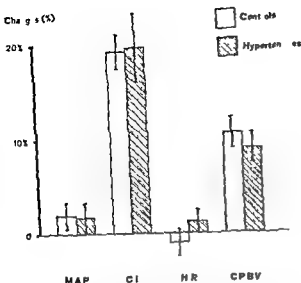


Fig 1 Changes in hemodynamic parameters before and after expansion in normotensive controls and hypertensive patients. Basal absolute values are indicated in Table II. MAP = mean arterial pressure. CI = cardiac index. HR = heart rate. CPBV = cardiopulmonary blood volume.

subtracted from the observed time in calculating MTT.

Before the hemodynamic study, total blood and plasma volumes were measured in the recumbent position by the isotopic dilution method using radioiodinated albumin as previously described. After withdrawal of a control sample 3  $\mu$ Ci were injected. Ten minutes later a sample was taken for radioactivity to be counted. Blood volume was normalized for body surface area.<sup>1</sup>

**Effective vascular compliance.** The study was performed in the supine position with a room temperature between 23 and 25 °C. The procedure was a modification of that described by Echt and associates. Effective compliance was determined during blood volume expansion using a dextran infusion. In order to minimize secondary effects due to capillary filtration and delayed compliance the study was carried out in the shortest possible time. Five hundred ml of 6 per cent dextran were infused within 4 minutes by a Sogreath MP 66 pump. Cardiac output and cardiopulmonary blood volume were remeasured at the end of the infusion. Central venous pressure was recorded during expansion and plotted against the volume (V) changes. The pressure-volume relationship was practically linear.

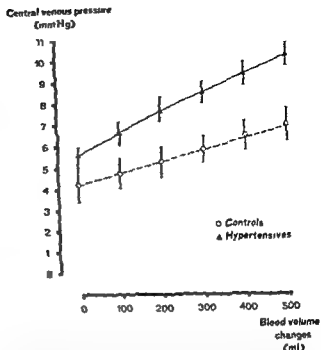


Fig 2 Relationship between blood volume changes and central venous pressure in normal subjects and hypertensive patients. Each point corresponds to the mean value of the group ( $\pm 1$  standard error of the mean).

Elasticity coefficient (E) of the total vascular bed was calculated as the slope of the relationship. Vascular compliance (1/E) was estimated and standardized to body weight. The reproducibility of the method was tested in five patients 3 days later. The mean variation was 6.3 per cent. In three other patients the volume expansion was followed by the withdrawal of the same amount of blood. As in the report by Echt and colleagues,<sup>1</sup> the slope of the pressure-volume relationship was practically identical during expansion and hemorrhage.

Statistical analysis by classical methods (differences of means, correlations, stepwise regression) was performed on an HP 9805 A calculator.

## Results

**Hemodynamic parameters (Table II).** Blood pressure and total peripheral resistance were elevated ( $p < 0.001$ ) in hypertensive patients. Heart rate, cardiac index, stroke index, and right atrial pressure were within normal ranges. Cardiopulmonary blood volume was normal.



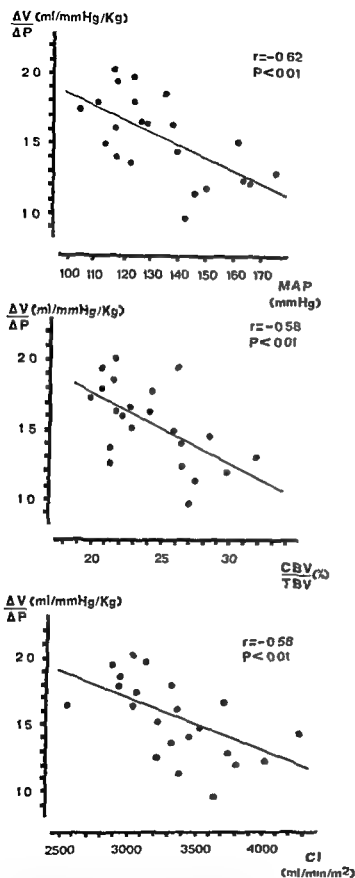


Fig 3 Relationships between the effective compliance ( $\Delta V / \Delta P$ ) and respectively mean arterial pressure (MAP) the ratio between cardiopulmonary (CBV) and total blood volume (TBV) and cardiac index (CI) in hypertensive patients.

while total blood volume was reduced significantly

**Effective vascular compliance** (Figs 1 and 2 Table III) Blood volume expansion induced no change in blood pressure or in heart rate (Fig 1) Increases in cardiac index and cardiopulmonary blood volume were similar in magnitude both in normal subjects and hypertensive patients (Fig 1) Fig 2 indicates the changes in central venous pressure related to the dextran infusion The intercept of the pressure-volume curves were not significantly different but the slope of the hypertensive group was steeper Effective vascular compliance was significantly reduced in hypertensive patients ( $1.55 \pm 0.60$  vs  $2.55 \pm 0.11$  ml/mm Hg/Kg in control subjects ( $p < 0.001$ ) Table III and Fig 3 demonstrate strong negative correlations between effective compliance and mean blood pressure ( $r = -0.62$ ,  $p < 0.01$ ) cardiac index ( $r = -0.58$ ,  $p < 0.01$ ) cardiopulmonary blood volume ( $r = -0.45$ ,  $p < 0.05$ ), and the ratio between cardiopulmonary and total blood volume ( $r = -0.58$ ,  $p < 0.01$ ) No comparable results were observed in control subjects

#### Comments

In the control subjects of the present study, the value of the effective compliance was in agreement with previous reports.<sup>7,8</sup> In the permanent hypertensive patients it was significantly decreased During the dextran infusion a change in blood pressure and/or an altered compliance of the heart did not seem to influence the result congestive heart failure was absent basal central venous pressures were within normal ranges during expansion cardiac output and cardiopulmonary blood volume increased in the same magnitude as in normal subjects Since the arterial system is an insignificant fraction of effective compliance the compliance of the total circulation is mainly related to the properties of the venous side of the circulation So the decreased compliance in hypertensive patients strongly suggests the existence of a reduced venous distensibility as previously observed in experimental hypertension<sup>11,12</sup> and in spontaneous hypertension in rats<sup>13,14</sup>

Since the veins are not exposed to the high pressure associated with arterial hypertension decreased venous compliance is unlikely to be

secondary to increased intraluminal pressure. However one of the major findings of the study was the strong relationship between compliance and pressure: the higher the blood pressure the lower the compliance. This correlation suggests that the decreased compliance results from some structural or functional influences common to both arterial and venous bed. Genetic differences<sup>1</sup> and/or abnormalities of the ionic and water content of vascular walls<sup>2</sup> have been said to induce structural changes in experimental hypertension and in spontaneous hypertension in rats. These defects are not only confined to the arteries. Recently they have also been observed in the venous capacitance vessels.<sup>17</sup> However the reduced venous distensibility cannot result solely from irreversible structural changes in the presence of effective antihypertensive therapy.<sup>2, 18</sup> Venous distensibility has been shown to return towards normal values. This would suggest the influence of neurogenic and/or hormonal factors. In favor of this is the decreased effective compliance induced by increased sympathetic activity or elevated levels of norepinephrine.<sup>2, 9</sup>

Whatever the factors involved changes in venous compliance have important consequences on the over all circulation. The decreased distensibility produces a redistribution of blood volume resulting in a shift of blood to the central circulation with a consequent increase in the filling pressure of the heart and an increase in cardiac output.<sup>1</sup> In the present study the strong negative relationship between the total body compliance and cardiac output, cardiopulmonary blood volume and the ratio between cardiopulmonary and total blood volume are additional evidence. In borderline hypertension increased venous return to the heart due to decreased venous compliance may help to account for the increased cardiac output found in these patients.<sup>1</sup> In permanent hypertension where blood volume is reduced the decreased compliance may maintain normal cardiac output. Thus hypertension should no longer be considered as confined to alterations in the arterial system. Changes in the venous bed also exist and require further investigations.

# Summary

Total effective vascular compliance, hemodynamic parameters, cardiopulmonary (CPBV) and

total blood volumes (TBV) were determined in 31 men including nine normotensive controls and 22 permanent essential hypertensive patients. The effective compliance was calculated from the changes in central venous pressure recorded simultaneously with the changes in blood volume obtained after a rapid dextran infusion. In hypertensives compliance was significantly reduced ( $155 \pm 0.6$  vs  $225 \pm 0.11$  ml/mm Hg/kg in controls) ( $P < 0.001$ ) and negatively correlated with blood pressure ( $P < 0.01$ ), cardiac index ( $P < 0.01$ ) and the CPBV/TBV ratio ( $P < 0.01$ ). These results suggest that venous compliance contributes to the control of cardiac output in essential hypertension.

Our thanks are extended to Mrs. C. Pillet for her technical assistance and to Miss A. Mangin who has been responsible for the secretarial work.

# REFERENCES

1. Shepherd J T. Role of the veins in the circulation. *Circulation* 33:484, 1966.
2. Walsh, J A. Hyman C and Maronde R P. Venous distensibility in essential hypertension. *Cardiovasc Res* 3:338, 1969.
3. Caliva F S, Napodano R J, Stafford R M, Loftus W., and Lyons, R H. Digital hemodynamics in the normotensive and hypertensive states. I. Digital mean arterial and venous pressures, blood flow and vascular resistance. *Circulation* 28:415, 1963.
4. Guyton A C. Venous return. In *Handbook of Physiology*, sec 2, vol 2. *Circulation*, edited by W F Hamilton and P Dow. Washington 1963. American Physiology Society pp 1099-1133.
5. Guyton A C, Polizo D and Armstrong G G. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 170:761, 1954.
6. Henry J P, Gauer O H and Sieker H O. Effect of moderate changes in blood volume on left and right atrial pressures. *Circ Res* 4:91, 1956.
7. Gauer O H, Henry J P and Sieker H O. Changes in central venous pressure after moderate hemorrhage and transfusion in man. *Circ Res* 4:79, 1956.
8. Echt M, Duweling J, Gauer O H., and Lange L. Effective compliance of the total vascular bed and the intrathoracic compartment derived from changes in central venous pressure induced by volume changes in man. *Circ Res* 33:61, 1974.
9. Safar M E, Weiss Y A., Levenson J A, London G M and Milliez P L. Hemodynamic study of 85 borderline hypertensive patients. *Am J Cardiol* 31:31, 1973.
10. Safar M E, Weiss Y A, London G M, Frackowiak R F and Milliez P L. Cardiopulmonary blood volume in borderline hypertension. *Clin Sci* 47:153, 1974.
11. Croxon F W and Cowden D J. Applied general statistics. New York 1944. Prentice Hall, Inc. p 41.
12. Ferraro C M, Page I H and McCubbin J W. Increased cardiac output as a contributory factor in

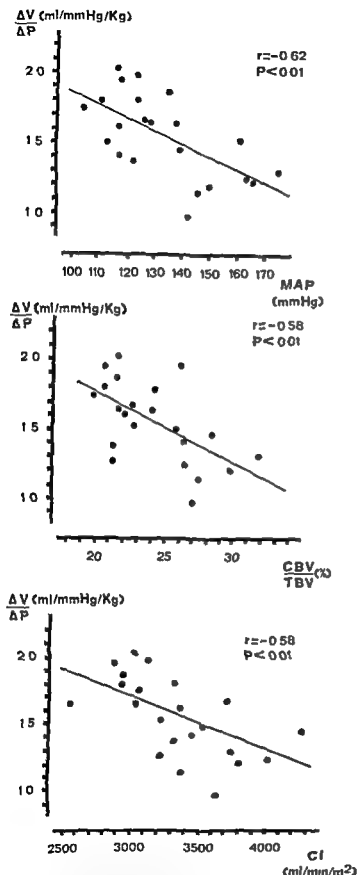


Fig 3 Relationships between the effective compliance ( $\Delta V / \Delta P$ ) and respectively mean arterial pressure (MAP) the ratio between cardiopulmonary (CBV) and total blood volume (TBV) and cardiac index (CI) in hypertensive patients.

while total blood volume was reduced significantly

**Effective vascular compliance** (Figs 1 and 2 Table III) Blood volume expansion induced no change in blood pressure or in heart rate (Fig 1) Increases in cardiac index and cardiopulmonary blood volume were similar in magnitude both in normal subjects and hypertensive patients (Fig 1) Fig 2 indicates the changes in central venous pressure related to the dextran infusion The intercept of the pressure-volume curves were not significantly different but the slope of the hypertensive group was steeper Effective vascular compliance was significantly reduced in hypertensive patients ( $1.55 \pm 0.60$  vs  $2.55 \pm 0.11$  ml/mm Hg/Kg in control subjects, ( $p < 0.001$ ) Table III and Fig 3 demonstrate strong negative correlations between effective compliance and mean blood pressure ( $r = -0.62$ ,  $p < 0.01$ ) cardiac index ( $r = -0.58$ ,  $p < 0.01$ ), cardiopulmonary blood volume ( $r = -0.45$ ,  $p < 0.05$ ), and the ratio between cardiopulmonary and total blood volume ( $r = -0.58$ ,  $p < 0.01$ ) No comparable results were observed in control subjects

### Comments

In the control subjects of the present study, the value of the effective compliance was in agreement with previous reports.<sup>1-4</sup> In the permanent hypertensive patients it was significantly decreased During the dextran infusion a change in blood pressure and/or an altered compliance of the heart did not seem to influence the result congestive heart failure was absent basal central venous pressures were within normal ranges during expansion cardiac output and cardiopulmonary blood volume increased in the same magnitude as in normal subjects Since the arterial system is an insignificant fraction of effective compliance<sup>1</sup> the compliance of the total circulation is mainly related to the properties of the venous side of the circulation So the decreased compliance in hypertensive patients strongly suggests the existence of a reduced venous distensibility as previously observed in experimental hypertension<sup>11,12,13</sup> and in spontaneous hypertension in rats<sup>14,15</sup>

Since the veins are not exposed to the high pressure associated with arterial hypertension decreased venous compliance is unlikely to be

secondary to increased intraluminal pressure. However one of the major findings of the study was the strong relationship between compliance and pressure: the higher the blood pressure the lower the compliance. This correlation suggests that the decreased compliance results from some structural or functional influences common to both arterial and venous bed. Genetic differences<sup>1</sup> and/or abnormalities of the ionic and water content of vascular walls have been said to induce structural changes in experimental hypertension and in spontaneous hypertension in rats. These defects are not only confined to the arteries. Recently they have also been observed in the venous capacitance vessels.<sup>2</sup> However the reduced venous distensibility cannot result solely from irreversible structural changes in the presence of effective antihypertensive therapy.<sup>3,4</sup> Venous distensibility has been shown to return towards normal values. This would suggest the influence of neurogenic and/or hormonal factors. In favor of this is the decreased effective compliance induced by increased sympathetic activity or elevated levels of norepinephrine.<sup>5,6</sup>

Whatever the factors involved changes in venous compliance have important consequences on the overall circulation. The decreased distensibility produces a redistribution of blood volume resulting in a shift of blood to the central circulation with a consequent increase in the filling pressure of the heart and an increase in cardiac output.<sup>7</sup> In the present study the strong negative relationship between the total body compliance and cardiac output, cardiopulmonary blood volume and the ratio between cardiopulmonary and total blood volume are additional evidence. In borderline hypertension increased venous return to the heart due to decreased venous compliance may help to account for the increased cardiac output found in these patients.<sup>8</sup> In permanent hypertension where blood volume is reduced the decreased compliance may maintain normal cardiac output. Thus hypertension should no longer be considered as confined to alterations in the arterial system. Changes in the venous bed also exist and require further investigations.

### Summary

Total effective vascular compliance, hemodynamic parameters, cardiopulmonary (CPBV) and

total blood volumes (TBV) were determined in 31 men including nine normotensive controls and 22 permanent essential hypertensive patients. The effective compliance was calculated from the changes in central venous pressure recorded simultaneously with the changes in blood volume obtained after a rapid dextran infusion. In hypertensives compliance was significantly reduced ( $1.55 \pm 0.6$  vs  $2.25 \pm 0.11$  ml/mm Hg/kg in controls) ( $P < 0.001$ ) and negatively correlated with blood pressure ( $P < 0.01$ ), cardiac index ( $P < 0.01$ ) and the CPBV/TBV ratio ( $P < 0.01$ ). These results suggest that venous compliance contributes to the control of cardiac output in essential hypertension.

Our thanks are extended to Mrs C. Pillet for her technical assistance and to Miss A. Mangin who has been responsible for the secretarial work.

### REFERENCES

1. Shepherd J T. Role of the veins in the circulation. *Circulation* 33:484, 1966.
2. Walsh, J. A., Hyman, C. and Merson-Davies, R. E. Venous distensibility in essential hypertension. *Cardiovasc Res* 3:338, 1969.
3. Caliva, F. S., Napodano, R. J., Stafford, W. M., Loftus, W. and Lyons, R. H. Digital hemodynamics in the normotensive and hypertensive states. I. Digital mean arterial and venous pressures, blood flow and vascular resistance. *Circulation* 28:415, 1963.
4. Guyton, A. C. Venous return. In *Handbook of Physiology*, sec. 2, vol. 11, *Circulation*, edited by W. F. Hamilton and P. Dow. Washington, 1963. American Physiology Society, pp. 1099-1133.
5. Guyton, A. C., Polizo, D. and Armstrong, G. G. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 179:261, 1954.
6. Henry, J. B., Gauer, O. H. and Sieker, H. O. Effect of moderate changes in blood volume on left and right atrial pressures. *Circ Res* 4:91, 1956.
7. Gauer, O. H., Henry, J. B., and Sieker, H. O. Changes in central venous pressure after moderate hemorrhage and transfusion in man. *Circ Res* 4:79, 1956.
8. Ediz, M., Dusseling, J., Gauer, O. H., and Lange, L. Effective compliance of the total vascular bed and the intrathoracic compartment derived from changes in central venous pressure induced by volume changes in man. *Circ Res* 33:61, 1974.
9. Safar, M. E., Weiss, Y. A., Levinson, J. A., London, G. M., and Milliez, P. L. Hemodynamic study of 85 borderline hypertensive patients. *Am J Cardiol* 31:315, 1973.
10. Safar, M. E., Weiss, Y. A., London, G. M., Frackowiak, R. F., and Milliez, P. L. Cardiopulmonary blood volume in borderline hypertension. *Clin Sci* 47:153, 1974.
11. Croxon, F. W., and Cowden, H. J. *Applied general statistics*, New York, 1944. Prentice Hall Inc, p. 41.
12. Ferraro, C. M., Page, I. H., and McCubbin, J. W. Increased cardiac output as a contributory factor in

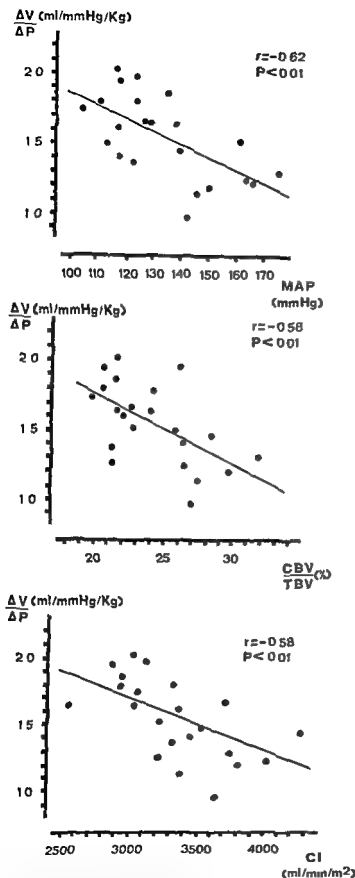


Fig 3 Relationships between the effective compliance ( $\Delta V/\Delta P$ ) and respectively mean arterial pressure (MAP) the ratio between cardiopulmonary (CBV) and total blood volume (TBV) and cardiac index (CI) in hypertensive patients

while total blood volume was reduced significantly

**Effective vascular compliance** (Figs 1 and 2 Table III) Blood volume expansion induced no change in blood pressure or in heart rate (Fig 1) Increases in cardiac index and cardiopulmonary blood volume were similar in magnitude both in normal subjects and hypertensive patients (Fig 1) Fig 2 indicates the changes in central venous pressure related to the dextran infusion The intercept of the pressure-volume curves were not significantly different but the slope of the hypertensive group was steeper Effective vascular compliance was significantly reduced in hypertensive patients ( $1.55 \pm 0.60$  vs  $2.55 \pm 0.11$  ml/mm Hg/Kg in control subjects ( $p < 0.001$ ) Table III and Fig 3 demonstrate strong negative correlations between effective compliance and mean blood pressure ( $r = -0.62$   $p < 0.01$ ) cardiac index ( $r = -0.58$ ,  $p < 0.01$ ) cardiopulmonary blood volume ( $r = -0.45$   $p < 0.05$ ) and the ratio between cardiopulmonary and total blood volume ( $r = -0.58$ ,  $p < 0.01$ ) No comparable results were observed in control subjects

### Comments

In the control subjects of the present study the value of the effective compliance was in agreement with previous reports.<sup>11</sup> In the permanent hypertensive patients it was significantly decreased During the dextran infusion a change in blood pressure and/or an altered compliance of the heart did not seem to influence the result congestive heart failure was absent basal central venous pressures were within normal ranges during expansion cardiac output and cardiopulmonary blood volume increased in the same magnitude as in normal subjects Since the arterial system is an insignificant fraction of the effective compliance the compliance of the total circulation is mainly related to the properties of the venous side of the circulation So the decreased compliance in hypertensive patients strongly suggests the existence of a reduced venous distensibility as previously observed in experimental hypertension<sup>12,13</sup> and in spontaneous hypertension in rats.<sup>14</sup>

Since the veins are not exposed to the high pressure associated with arterial hypertension decreased venous compliance is unlikely to be

secondary to increased intraluminal pressure. However, one of the major findings of the study was the strong relationship between compliance and pressure: the higher the blood pressure, the lower the compliance. This correlation suggests that the decreased compliance results from some structural or functional influences common to both arterial and venous bed. Genetic differences and/or abnormalities of the ionic and water content of vascular walls have been said to induce structural changes in experimental hypertension and in spontaneous hypertension in rats. These defects are not only confined to the arteries. Recently they have also been observed in the venous capacitance vessels. However, the reduced venous distensibility cannot result solely from irreversible structural changes in the presence of effective antihypertensive therapy. Venous distensibility has been shown to return towards normal values. This would suggest the influence of neurogenic and/or hormonal factors. In favor of this is the decreased effective compliance induced by increased sympathetic activity or elevated levels of norepinephrine.<sup>2, 3</sup>

Whatever the factors involved, changes in venous compliance have important consequences on the overall circulation. The decreased distensibility produces a redistribution of blood volume resulting in a shift of blood to the central circulation with a consequent increase in the filling pressure of the heart and an increase in cardiac output. In the present study, the strong negative relationship between the total body compliance and cardiac output, cardiopulmonary blood volume and the ratio between cardiopulmonary and total blood volume are additional evidence. In borderline hypertension, increased venous return to the heart due to decreased venous compliance may help to account for the increased cardiac output found in these patients.<sup>4</sup> In permanent hypertension, where blood volume is reduced, the decreased compliance may maintain normal cardiac output. Thus, hypertension should no longer be considered as confined to alterations in the arterial system. Changes in the venous bed also exist and require further investigations.

### Summary

Total effective vascular compliance, hemodynamic parameters, cardiopulmonary (CPBV) and

total blood volumes (TBV) were determined in 31 men including nine normotensive controls and 22 permanent essential hypertensive patients. The effective compliance was calculated from the changes in central venous pressure recorded simultaneously with the changes in blood volume obtained after a rapid dextran infusion. In hypertensives, compliance was significantly reduced ( $1.55 \pm 0.6$  vs  $2.25 \pm 0.11$  ml/mm Hg/kg in controls) ( $P < 0.001$ ) and negatively correlated with blood pressure ( $P < 0.01$ ), cardiac index ( $P < 0.01$ ) and the CPBV/TBV ratio ( $P < 0.01$ ). These results suggest that venous compliance contributes to the control of cardiac output in essential hypertension.

Our thanks are extended to Mrs. C. Pillet for her technical assistance and to Miss A. Mangin who has been responsible for the secretarial work.

### REFERENCES

1. Shepherd J. T. Role of the veins in the circulation. *Circulation* 33:484, 1966.
2. Walsh, J. A., Hyman, C. and Maronde, R. F. Venous distensibility in essential hypertension. *Cardiovasc Res* 3:338, 1969.
3. Caliva, F. S., Napodano, R. J., Stafford, R. M., Loftus, W. and Lyons, R. H. Digital hemodynamics in the normotensive and hypertensive states. I. Digital mean arterial and venous pressures, blood flow and vascular resistance. *Circulation* 28:415, 1963.
4. Guyton, A. C. Venous return. In *Handbook of Physiology*, sec. 2, vol. 2, Circulation, edited by W. F. Hamilton and P. Dow. Washington, 1963. American Physiology Society, pp. 1099-1133.
5. Guyton, A. C., Polzo, D. and Armstrong, G. G. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am. J. Physiol.* 179:261, 1954.
6. Henry, J. P., Gauer, O. H. and Sieker, H. O. Effect of moderate changes in blood volume on left and right atrial pressures. *Circ. Res.* 4:91, 1956.
7. Gauer, O. H., Henry, J. P., and Sieker, H. O. Changes in central venous pressure after moderate hemorrhage and transfusion in man. *Circ. Res.* 4:79, 1956.
8. Echt, M., Duwelning, J., Gauer, O. H. and Lange, L. Effective compliance of the total vascular bed and the intrathoracic compartment derived from changes in central venous pressure induced by volume changes in man. *Circ. Res.* 33:61, 1974.
9. Safar, M. E., Weiss, Y. A., Levenson, J. A., London, G. M. and Milliez, P. L. Hemodynamic study of 85 borderline hypertensive patients. *Am. J. Cardiol.* 31:315, 1973.
10. Safar, M. E., Weiss, Y. A., London, G. M., Frackowiak, R. F. and Milliez, P. L. Cardiopulmonary blood volume in borderline hypertension. *Clin. Sci.* 47:153, 1974.
11. Croxon, F. W. and Cowden, J. Applied general statistics. New York, 1944. Prentice Hall, Inc., p. 41.
12. Ferrario, C. M., Pag, I. H. and McCubbin, J. W. Increased cardiac output as a contributory factor in

- experimental renal hypertension in dogs *Circ Res* 27 799 1970
- 13 Simon G Pamnani M B Dunkel J F and Overbeck H W Mesenteric hemodynamics in early experimental renal hypertension in dogs *Circ Res* 36 791 1975
- 14 Grunberg S and Bohr D F Venous smooth muscle in hypertension enhanced contractility of portal veins from spontaneously hypertensive rats *Circ Res* 36 208 1975
- 15 Simon G Altered venous function in hypertensive rats *Circ Res* 38 412 1976
- 16 Tobian L Interrelationship of electrolytes juxtaglomerular cells and hypertension *Physiol Rev* 40 280 1960
- 17 Pamnani M B and Overbeck H W Abnormal ion and water composition of veins and normotensive arteries in coarctation hypertension in rats *Circ Res* 38 373 1976
- 18 Mason D T and Braunwald E Effects of guanethidine reserpine and methyldopa on reflex venous and arterial constriction in man *J Clin Invest* 43 1449 1964
- 19 Urych M Frohlich E D Tarazi H C Dustan H P and Page I H Cardiac output and distribution of blood volume in central and peripheral circulations in hypertensive and normotensive man *Br Heart J* 31 50 1969
- 20 Julius S Pascual A V Reilly K and London R Abnormalities of plasma volume in borderline hypertension *Arch Intern Med* 127 116 1971

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center Inc. P.O. Box 765, Schenectady, N.Y. 12301 518 374-4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

# Effect of pentobarbital anesthesia on ventricular defibrillation threshold in dogs

Charles F Babbs MD MS\*  
West Lafayette Ind

Electric shock applied across the chest or directly to the heart is the only practicable means for termination of ventricular fibrillation an other wise lethal cardiac arrhythmia The shock strength required for defibrillation of the ventricles depends upon body weight in animals and in man\* but also may be influenced by physiologic factors such as myocardial ischemia electrolyte imbalance drug action and body temperature\*\* Knowledge of the factors which determine the shock strength necessary for defibrillation is important because a shock which is too weak may fail to defibrillate and a shock which is too strong may damage the heart \*

All controlled experimental studies of electrical ventricular defibrillation reported to date have used anesthetized animals as subjects—in most cases barbiturate anesthetized dogs In contrast virtually all clinical ventricular defibrillations outside the operating room are carried out in unanesthetized patients in settings such as the coronary care unit or emergency room Recently the barbiturate anesthetized dog has been criticized as a model of normal cardiovascular physiology<sup>1</sup> Since no study can be found in the literature reporting the influence of anesthesia on

the efficacy of electrical defibrillation a reasonable question may be raised about the validity of anesthetized animal models used for defibrillation studies

The author has reviewed 58 reports dated 1899 to 1975 concerning the efficacy of electric shock for the termination of cardiac fibrillation in animals In only one study was no anesthesia employed routinely In 27 of 58 studies injectable pentobarbital sodium was the only anesthetic used in a particular species In 10 of the studies thiopental sodium was employed either alone or in combination with inhalation anesthetics and muscle relaxants In six of the studies a mixture of halothane nitrous oxide and oxygen was used often after the induction of anesthesia with intravenous thiopental sodium The use of a variety of other anesthetic agents for defibrillation studies has been reported including sodium barbital glycerol guaiacolate morphine and chloralose In 52 of the 58 studies dogs were used as experimental subjects In particular the pentobarbital anesthetized dog was used in 36 (62 per cent) of the defibrillation studies

Unquestionably anesthetic agents of all kinds have direct effects upon excitable biologic membranes Although the central nervous system is the most important site of action of general anesthetic agents many anesthetics including pentobarbital are known to affect the mechanical and electrical performance of cardiac muscle The amplitude and strength of myocardial contraction are depressed by cyclopropane, diethyl ether nitrous oxide and halothane as well as by barbiturates including pentobarbital secobarbital and thiopental<sup>2</sup> Hydrocarbon anesthetics may depress the rate of activity of the sinus node pacemaker as well as the speed of AV

From Purdue University Biomedical Engineering Center and the Department of Pharmacy and Toxicology Purdue University West Lafayette Ind.

Supported in part by grant HL-1 855-03 from the National Heart and Lung Institute National Institutes of Health, Bethesda Md.

Received for publication July 7 1977

Accepted for publication Aug 1 1977

Reprint requests: Charles F Babbs, MD, Institute for Interdisciplinary Engineering Studies, Biomedical Engineering Center, Room 204 A, A. P. Ter Engineering Bldg, Purdue University, West Lafayette Ind. 47907

D Babbs was supported by a Fellowship Grant from the American Heart Association, Indiana Affiliate, Inc.



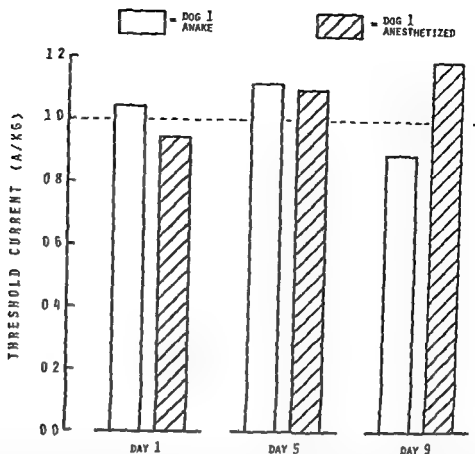


Fig 1 Threshold peak current for ventricular defibrillation in unanesthetized and anesthetized states on successive trials in the same animal. On three successive trials the threshold current in the unanesthetized animal was greater than equal to and less than the threshold current after induction of pentobarbital anesthesia. Mean threshold before anesthesia = 1.02 A/Kg. Mean threshold after anesthesia = 1.08 A/Kg. Threshold data for the unanesthetized dog were reproducible within  $\pm 10$  per cent limits.

and intraventricular conduction<sup>13-17</sup> Significant differences in the response of the dog heart to the AV blocking and arrhythmogenic actions of digitalis glycosides have been reported for animals anesthetized with pentobarbital vs halothane, vs methoxyflurane<sup>18</sup> Cyclopropane halothane and to a lesser extent thiopental are known to sensitize the myocardium to the arrhythmogenic effects of epinephrine<sup>19</sup> Accordingly, it is quite conceivable that anesthetics could alter those parameters of cardiac electrophysiology which determine the success or failure of electrical defibrillation.

It is generally accepted that during the induction of anesthesia the relative lipid solubility of general anesthetics and the generous blood flow to the brain cause initial concentration of these drugs in the central nervous system. After maintenance of anesthesia for several minutes to several hours, however, these drugs become widely redistributed in peripheral tissues including the myocardium<sup>20-22</sup> If there were a significant effect of anesthetics upon the determinants

of electrical defibrillation one might reasonably expect a gradual drift of the threshold voltage and current for defibrillation over the course of experiments using anesthetized animals as subjects. Control studies demonstrating the presence or absence of such a drift in defibrillation threshold over time intervals greater than one hour have not been reported to date.

Accordingly the following studies were undertaken to determine (1) if the induction of anesthesia with intravenous pentobarbital sodium in the dog alters transchest defibrillation threshold and (2) if the maintenance of a stable surgical level of anesthesia with pentobarbital sodium for 1 to 10 hours is associated with a change in the defibrillation threshold.

#### Methods

**Study 1 Effect of pentobarbital anesthesia**  
Five dogs of mixed breed weighing 8 to 14 kilograms served as subjects. Initially each dog was anesthetized with injectable pentobarbital sodium (Nembutal 50 mg/ml in a 10 per cent

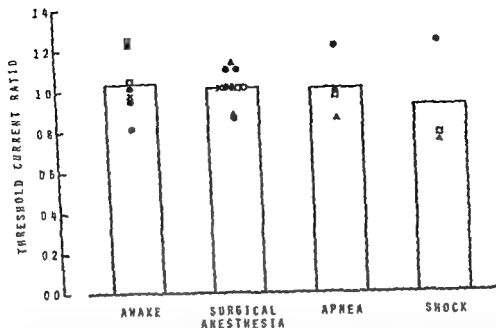


Fig 2 Relative values of threshold peak current for ventricular defibrillation at four levels of anesthesia. Awake = no anesthesia; surgical anesthesia = spontaneous respiration but no response to surgical stimulation (25 to 30 mg/Kg pentobarbital); apnea = no spontaneous respiration (42 to 51 mg/Kg pentobarbital, cumulative dose); shock = aortic blood pressure less than 50 mm Hg systolic (61 to 77 mg/kg pentobarbital, cumulative dose). Mean threshold current under surgical anesthesia = 1.0 for each animal. Dog 1 solid circles; Dog 2, solid triangles; Dog 3 open circles; Dog 4 open squares; Dog 5 crosses.

alcohol 40 per cent propylene glycol vehicle 25 to 30 mg/Kg intravenously). No preanesthetic medication was given. A bipolar catheter electrode was placed in the right ventricle of the heart via a right jugular venous cut down using sterile technique. Position of the catheter electrode within the heart was verified by recording the catheter tip electrogram and comparing its timing with the electrocardiogram (ECG) Lead II. The catheter was stabilized in the jugular vein and the wound was closed with 2.0 silk sutures. The external portion of the catheter was protected with an adhesive elastic bandage placed around the neck and a soft collar 8 cm in width. After a recovery period of 36 to 72 hours the defibrillation threshold was determined before and after induction of anesthesia with pentobarbital. These investigations in unanesthetized and anesthetized subjects were carried out in accordance with National Institutes of Health and institutional guidelines for the use of laboratory animals.

Defibrillation threshold in awake unrestrained animals was measured as follows. ECG Lead II electrodes were applied to the limbs and the position of the catheter electrode was confirmed

by recording the catheter tip electrogram. Defibrillating electrodes held in position with rubber straps were applied to the shaved skin of the thorax with electrolytic jelly, one centered over the apex beat area and the other in the opposite position on the right chest wall. The defibrillating electrodes were stainless steel discs 2 mm thick and 8 to 10 cm in diameter (28 per cent of the animal's chest circumference  $\pm$  1 cm). The standard location of each electrode was outlined in ink on the thorax.

Ventricular fibrillation was produced by the application of a 1 second train of 60 Hz m.e.c duration rectangular electrical pulses of 5 to 15 volts intensity via the right ventricular catheter. Ventricular fibrillation was confirmed by the presence of random waves in the electrocardiogram and by the descending level of consciousness of the subject. As the animal lost consciousness it was placed in dorsal recumbency.

The defibrillator employed contained a 16 microfarad capacitance, a 44 millihenry inductance and a 7 ohm internal resistance in series with the subject. A 100 ohm 100 watt resistor in series with one electrode was used for measuring

current output. The peak output voltage of the defibrillator could be varied continuously from 0 to 7,000 volts. The duration of the delivered current pulse, slightly dependent upon subject resistance, was typically 4 to 5 msec. The wave form of the current pulse was a heavily damped sinusoid.

As soon as possible after the confirmation of ventricular fibrillation, (15 to 45 seconds after endocardial stimulation) a defibrillator shock, calculated to be adequate for defibrillation on the basis of the dog's body weight as described by Geddes and colleagues,<sup>2</sup> was delivered at the time of end expiration. The voltage and current applied to the subject were measured using a Tektronics model D 11 dual channel storage oscilloscope. Defibrillation was confirmed by return of the femoral pulse and QRS complexes in the electrocardiogram. With return of consciousness the animal was allowed to right itself. After a recovery period of about 2 minutes the animal was re fibrillated and defibrillation was attempted with a voltage setting 5 to 10 per cent less than that of the previous trial. This procedure was repeated until the animal was not defibrillated by the first shock, whereupon a stronger shock was applied immediately to restore cardiac pumping action. Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles. Only data from the first shock delivered after the onset of fibrillation were used in calculation of threshold. In this study threshold values were considered adequately precise if they differed no more than 10 per cent from values unable to defibrillate the ventricles. Delivered energy and charge were calculated as described by Babbs and Whistler.<sup>5</sup>

Twenty minutes after the defibrillation threshold was determined in the unanesthetized animal intravenous pentobarbital sodium (25 to 30 mg / Kg) was given to produce surgical anesthesia and the defibrillation threshold measurement was repeated with the animal in dorsal recumbency. After a three day recovery period another set of threshold determinations was made in the awake and anesthetized states.

On the final day of testing the defibrillation threshold was determined following larger doses of pentobarbital. After the routine threshold determination under surgical anesthesia sufficient intravenous pentobarbital was given to

produce apnea and the threshold measurement was repeated. Then sufficient intravenous pentobarbital was given to produce circulatory shock (defined as systolic blood pressure less than 50 mm Hg measured via a catheter placed in the abdominal aorta) and a final threshold determination made within 10 minutes. During apnea and shock the animal was maintained using mechanical ventilation sufficient to produce a respiratory minute volume measured with a Wright respirometer, roughly equal to that measured under surgical anesthesia.

**Study 2. Stability of defibrillation threshold under pentobarbital anesthesia.** Five dogs of mixed breed 5 to 16 kilograms in weight conditioned in captivity for a period of at least two weeks and disease free by physical examination were used in this study. Each animal was anesthetized with intravenous pentobarbital sodium (25 to 30 mg / Kg). No other drug except normal saline was administered at any time. The trachea was intubated and the animal placed in dorsal recumbency for the duration of the study. The urinary bladder was catheterized with a No. 8 French filiform catheter connected to a closed volumetric drainage bottle. Mean aortic blood pressure was measured using a mercury manometer, and respiratory minute volume was measured with a Wright respirometer. Arterial blood pH, pCO<sub>2</sub> and pO<sub>2</sub> were monitored using an Instrumentation Laboratories Model 213 blood gas analyzer. Disc electrodes of 8, 10 or 12 cm in diameter (20 per cent of the chest circumference  $\pm$  1 cm) were applied to the shaved skin of the right and left hemithoraces with electrolytic jelly and sutured in place. One electrode was centered over the apex beat of the heart and the other was located at a corresponding position on the right chest wall, 3 cm cephalad of the left electrode. Defibrillation threshold was determined once every hour using the method described for Study 1. The values of mean aortic blood pressure, respiratory minute volume, urine output, arterial blood gases and esophageal temperature were recorded at half hour intervals. A stable level of surgical anesthesia was maintained in each animal by the intravenous administration of 2 to 5 mg / Kg maintenance doses of pentobarbital sodium each hour. Saline solution 0.9 per cent was given in quantities of 1 to 2 ml / Kg / hr by vein. Esophageal temperature was maintained in

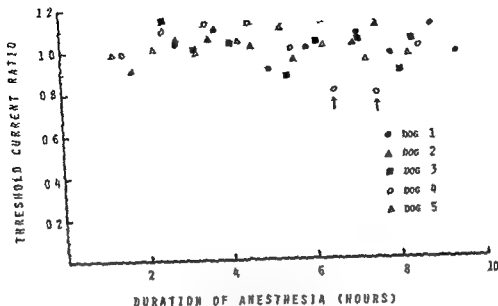


Fig 3 Stability of ventricular defibrillation threshold during pentobarbital anesthesia in dogs. Mean threshold current = 10 for each animal. Arrows indicate threshold values obtained during acute respiratory failure.

the range of 36 to 39 °C with the aid of warm overhead lights.

### Results

**Study 1** In all five dogs comparisons could be made between defibrillation thresholds in the awake and the anesthetized states. In one dog three successive comparisons of awake vs anesthetized threshold values were made during a 12 day period. Threshold current data for this animal are plotted in Fig 1. The ratios of the threshold peak current for all dogs at all levels of anesthesia to the average threshold under surgical anesthesia for each animal are plotted in Fig 2. No consistent effect of pentobarbital anesthesia on the ventricular fibrillation threshold is evident.

Mean values of threshold shock strength in terms of peak current, delivered energy, and delivered charge per kilogram of body weight are given in Table 1. One way analyses of variance indicate that the observed effects of anesthesia level upon threshold current, energy, and charge are far from statistically significant as indicated by the *p* values in the table.

The response of unanesthetized dogs to the fibrillation-defibrillation procedure is worthy of mention. Typically the dogs were not alarmed by the intracardiac electrical stimulation used to

induce fibrillation. The loss of cerebral blood flow due to ventricular fibrillation produced initial excitation lasting 5 to 15 seconds which rapidly diminished as the animal lost consciousness. Delivery of defibrillating current caused a brief forceful contraction of thoracic and abdominal musculature resulting in vocalization. Animals for whom the total circulatory arrest time was less than 30 seconds rapidly regained consciousness and assumed a sitting or standing position. Animals for whom the total circulatory arrest time was 30 to 60 seconds did not regain consciousness as soon after defibrillation. These animals remained in dorsal recumbency after resuscitation and appeared dazed or tranquilized.

**Study 2** Stability of defibrillation threshold during anesthesia. Fig 3 shows the relative threshold current values for five pentobarbital anesthetized dogs as a function of the duration of anesthesia. Relative threshold values were obtained by dividing each threshold current by the mean threshold value for a particular animal. No upward or downward drift of the threshold current is evident. The variation of individual threshold values seldom exceeds  $\pm 10$  per cent limits indicated by dotted lines. Interestingly the two extreme points in Fig 2 (Dog 4 arrows) were associated with a bout of acute respiratory

**current output** The peak output voltage of the defibrillator could be varied continuously from 0 to 7000 volts. The duration of the delivered current pulse slightly dependent upon subject resistance was typically 4 to 5 msec. The waveform of the current pulse was a heavily damped sinusoid.

As soon as possible after the confirmation of ventricular fibrillation, (15 to 45 seconds after endocardial stimulation), a defibrillator shock, calculated to be adequate for defibrillation on the basis of the dog's body weight as described by Geddes and colleagues<sup>2</sup> was delivered at the time of end expiration. The voltage and current applied to the subject were measured using a Tektronics model D 11 dual channel storage oscilloscope. Defibrillation was confirmed by return of the femoral pulse and QRS complexes in the electrocardiogram. With return of consciousness the animal was allowed to right itself. After a recovery period of about 2 minutes, the animal was re fibrillated and defibrillation was attempted with a voltage setting 5 to 10 per cent less than that of the previous trial. This procedure was repeated until the animal was not defibrillated by the first shock, whereupon a stronger shock was applied immediately to restore cardiac pumping action. Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles. Only data from the first shock delivered after the onset of fibrillation were used in calculation of threshold. In this study threshold values were considered adequately precise if they differed no more than 10 per cent from values unable to defibrillate the ventricles. Delivered energy and charge were calculated as described by Babbs and Whistler.<sup>3</sup>

Twenty minutes after the defibrillation threshold was determined in the unanesthetized animal intravenous pentobarbital sodium (25 to 30 mg / Kg), was given to produce surgical anesthesia and the defibrillation threshold measurement was repeated with the animal in dorsal recumbency. After a three day recovery period another set of threshold determinations was made in the awake and anesthetized states.

On the final day of testing the defibrillation threshold was determined following larger doses of pentobarbital. After the routine threshold determination under surgical anesthesia sufficient intravenous pentobarbital was given to

produce apnea and the threshold measurement was repeated. Then sufficient intravenous pentobarbital was given to produce circulatory shock (defined as systolic blood pressure less than 50 mm Hg measured via a catheter placed in the abdominal aorta) and a final threshold determination made within 10 minutes. During apnea and shock the animal was maintained using mechanical ventilation sufficient to produce a respiratory minute volume measured with a Wright respirometer, roughly equal to that measured under surgical anesthesia.

**Study 2 Stability of defibrillation threshold under pentobarbital anesthesia** Five dogs of mixed breed, 5 to 16 kilograms in weight, conditioned in captivity for a period of at least two weeks, and disease free by physical examination were used in this study. Each animal was anesthetized with intravenous pentobarbital sodium (25 to 30 mg / Kg). No other drug except normal saline was administered at any time. The trachea was intubated and the animal placed in dorsal recumbency for the duration of the study. The urinary bladder was catheterized with a No. 8 French filiform catheter connected to a closed volumetric drainage bottle. Mean aortic blood pressure was measured using a mercury manometer and respiratory minute volume was measured with a Wright respirometer. Arterial blood pH, pCO<sub>2</sub> and pO<sub>2</sub> were monitored using an Instrumentation Laboratories Model 213 blood gas analyzer. Disc electrodes of 8, 10 or 12 cm in diameter (20 per cent of the chest circumference  $\pm$  1 cm) were applied to the shaved skin of the right and left hemithoraces with electrolytic jelly and sutured in place. One electrode was centered over the apex beat of the heart and the other was located at a corresponding position on the right chest wall, 3 cm cephalad of the left electrode. Defibrillation threshold was determined once every hour using the method described for Study 1. The values of mean aortic blood pressure, respiratory minute volume, urine output, arterial blood gases and esophageal temperature were recorded at half hour intervals. A stable level of surgical anesthesia was maintained in each animal by the intravenous administration of 2 to 5 mg / Kg maintenance doses of pentobarbital sodium each hour. Saline solution 0.9 per cent was given in quantities of 1 to 2 ml / Kg / hr by vein. Esophageal temperature was maintained in

- ventricles following myocardial infarction *AM HEART J* 88 476 1974
- 7 Tacker W A Geddes L A Kline H and Borton C Alteration of electrical defibrillation threshold by the cardiac glycoside ouabain *Proceedings of the Cardiac Defibrillation Conference Purdue University West Lafayette Indiana* 1975 pp 129 133
- 8 Babbs C F Abendschein D R Tacker W A and Geddes L A Subject-dependent factors in ventricular defibrillation *Medical Instrumentation* 10 57 1976
- 9 Davis J E Lue J T Bentinck D C Titus J L Tacker W A and Geddes L A Cardiac damage due to electric current and energy *Proceedings of the Cardiac Defibrillation Conference Purdue University West Lafayette Indiana* 1975 pp 27-30
- 10 Dahl C Y Ewy G A Warner E D and Thomas E D Myocardial necrosis from direct current counter shock Effect of paddle electrode size and time interval between discharges *Circulation* 50 956 1974
- 11 Prano L L Traber H L and Wilson R D Barbiturate anesthesia an abnormal physiologic situation *J Pharmacol Exp Ther* 165 126 1969
- 12 Price H L and Helrich M The effect of cyclopropane diethyl ether nitrous oxide thiopental, and hydrogen ion concentration on the myocardial function of the dog heart lung preparation *J Pharmacol Exp Ther* 115 206 1955
- 13 Flacke W and Alper M H Actions of halothane and norepinephrine in the isolated mammalian heart *Anesthesiology* 23 793 1967
- 14 Hardman H F Moore J I and Lum B K B A method for analyzing the effect of pH and the ionization of drugs upon cardiac tissue with special reference to pentobarbital *J Pharmacol Exp Ther* 126 136 19 9
- 15 Effendi H Versprille A and Wise M E The negative inotropic effect of barbiturates on the heart of newborn and adult guinea pigs *Arch Int Pharma dyn* 209 127 1973
- 16 Etsten B and Li T H Hemodynamic changes during thiopental anesthesia in humans cardiac output stroke volume total peripheral resistance and intrathoracic blood volume *J Clin Invest* 34 500 1955
- 17 Smith S L Webb W R Sabian L W, and Hagaman V D Cardiac excitability in ether cyclopropane and halothane anesthesia *Anesthesiology* 23 766 1967
- 18 Morrow D H, Haley J V and Logan J H Anesthesia and digitalis VII The effect of pentobarbital, halothane and methoxyflurane on the AV conduction and inotropic responses to ouabain *Anesth Analg* 51 430 1970
- 19 Dresel P E Cyclopropane-epinephrine cardiac arrhythmias, in Price H L, and Cohen P J Effects of anesthetics on the circulation Springfield Illinois, 1964 Charles C Thomas
- 20 Brodie B B Boms J J Morc L C, Lief P A Burnstein E and Papper M M The fate of pentobarbital in man and dog and a method for its estimation in biological material, *J Pharmacol Exp Ther* 109 26 1953
- 21 Price H L, Hounst P J, Safer J N, Conner H, and Price M L The uptake of thiopental of body tissues and its relation to the duration of narcosis *Clin Pharmacol Ther* 1 16 1960
- 22 Goldstein A and Aronow L The durations of action of thiopental and pentobarbital, *J Pharmacol Exp Ther* 126 1 1960
- 23 Guide for the care and use of laboratory animals U S Department of Health Education and Welfare DHEW Pub No (NIH) 73 23 Revised 1977
- 24 Regulations for animal facilities and care Purdue University May 19 72
- 25 Babbs C F, and Whistler S J Evaluation of the operating internal resistance inductance and capacitance of intact damped sine wave defibrillators *Medical Instrumentation* (In press January 1978)

Table 1 Mean defibrillation threshold\* at 4 levels of anesthesia

|                                  | Awake    | Surgical anesthesia | Apnea    | Shock    | F ratio | P value |
|----------------------------------|----------|---------------------|----------|----------|---------|---------|
| Peak current (amps/Kg)           | 125 ± 38 | 122 ± 17            | 121 ± 18 | 113 ± 21 | 0.21    | 0.89    |
| Delivered energy (w s/Kg)        | 155 ± 77 | 135 ± 46            | 128 ± 42 | 111 ± 17 | 0.51    | 0.68    |
| Delivered charge (m coulombs/Kg) | 231 ± 41 | 218 ± 25            | 226 ± 43 | 206 ± 39 | 0.43    | 0.3     |
| Number of observations           | 7        | 11                  | 4        | 3        |         |         |

± 1 S D

failure (arterial blood gases pH 7.10, pCO<sub>2</sub> 54 mm Hg, pO<sub>2</sub> 39 mm Hg) after the institution of mechanical ventilation in this animal the threshold returned to control levels. With the exception of this incident all dogs exhibited a stable compensated metabolic acidosis. Arterial blood pH, pCO<sub>2</sub>, and pO<sub>2</sub> averaged 7.36 ± 0.06, 33 ± 3.7\* and 71 ± 9\* respectively. Mean arterial blood pressure, respiratory minute volume, and urine output were stable during the 8 to 10 hours of pentobarbital anesthesia in all five animals averaging 127 ± 20\* mm Hg, 457 ± 168\* ml/Kg/minute and 12 ± 0.5\* ml/Kg/hr, respectively.

### Discussion

The data of Studies 1 and 2 indicate that the ventricular defibrillation threshold is negligibly affected by either the induction or the maintenance of anesthesia with pentobarbital sodium. This finding is important because so many experimental studies of electrical defibrillation have been carried out in anesthetized animals whereas in most clinical situations electrical defibrillation is attempted in unanesthetized humans. In view of these results the extrapolation of much hard won animal data to the human situation may be made with significantly greater assurance.

In the absence of surgical or pharmacological intervention defibrillation threshold is a stable and reproducible parameter in the pentobarbital anesthetized dog. Demonstration of such a stable baseline paves the way for further studies of drug effects in ventricular defibrillation in the presence or absence of myocardial ischemia and for experimental evaluation of alternative techniques of cardiopulmonary resuscitation.

### Summary

The effect of pentobarbital anesthesia upon the minimal voltage and current required for elec-

trical ventricular defibrillation (the defibrillation threshold) was investigated in dogs. Threshold current, energy, and charge in five dogs averaged 2 per cent, 13 per cent, and 6 per cent less under surgical levels of pentobarbital anesthesia than thresholds in the same animals in the awake, unanesthetized state. In dogs given sufficient pentobarbital to produce apnea and supported by mechanical ventilation, threshold current, energy, and charge averaged 3 per cent, 17 per cent, and 2 per cent less than comparable awake values. These differences were far from statistically significant. In a second study five dogs were kept for 8 to 10 hours at a surgical level of anesthesia with pentobarbital sodium. Defibrillation threshold current determined at hourly intervals, did not drift outside ± 10 per cent limits. Arterial blood gas measurements revealed a stable compensated metabolic acidosis in all animals (pH 7.36 ± 0.06, pCO<sub>2</sub> 33 ± 4 mm Hg, pO<sub>2</sub> 71 ± 9 mm Hg). These data support the validity of defibrillation studies using animals anesthetized with pentobarbital and indicate the stability of the defibrillation threshold under controlled experimental conditions.

### REFERENCES

- Geddes L A. Electrical ventricular defibrillation. *Cardiovasc Res Center Bull* 10:3 1971.
- Geddes L A, Tacker W A, Rosborough J P, Moore A G, and Cabler P S. Electrical dose for ventricular defibrillation of large and small animals using precordial electrodes. *J Clin Invest* 53:310 1974.
- Geddes L A, Tacker W A, Rosborough J P, Moore A G, Cabler B S, Bailey M, McCrady J D, and Witzel D. The electrical dose for ventricular defibrillation with electrodes applied directly to the heart. *J Thorac Cardiovasc Surg* 68:593 1974.
- Tacker W A, Gahoto F M, Ghanian E, Geddes L A, and McNamara D G. Energy dose for human trans chest electrical ventricular defibrillation. *N Engl J Med* 290:214 1974.
- Gutgesell H P, Tacker W A, Geddes L A, Davis J D, Luc J T, and McNamara D G. Energy dose for ventricular defibrillation in children. *Pediatrics* 58:924 1977.
- Tacker W A, Geddes L A, Cabler P S, and Moore A G. Electrical threshold for defibrillation of canine

One standard deviation

- ventricles following myocardial infarction *AM HEART J* 88 416 1974
- 7 Tacker W A, Geddes L A, Kline B and Borton C Alteration of electrical defibrillation threshold by the cardiac glycoside ouabain *Proceedings of the Cardiac Defibrillation Conference Purdue University West Lafayette Indiana* 1975 pp 129 133
- 8 Babbs C F, Abendschein D R, Tacker W A and Geddes L A. Subj ect-dependent factors in ventricular defibrillation *Medical Instrumentation* 10 52, 1976
- 9 Davis J S, Lee J T, Bentinck D C, Titus J L, Tacker W A and Geddes L A. Cardiac damage due to electric current and energy *Proceedings of the Cardiac Defibrillation Conference Purdue University West Lafayette Indiana* 1975 pp 27 32
- 10 Dahl, C F., Ewy G A, Warner E D and Thomas F D. Myocardial necrosis from direct current counter shock. Effect of paddle electrode size and time interval between discharges *Circulation* 50 956 1974
- 11 Priano L L, Traber D L and Wilson R D. Barbiturate anesthesia: an abnormal physiologic situation *J Pharmacol Exp Ther* 165 176 1969
- 12 Price H L and Helrich M. The effect of cyclopropane, diethyl ether, nitrous oxide, thiopental and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation *J Pharmacol Exp Ther* 115 206 1955
- 13 Flacke W and Alper M H. Actions of halothane and norepinephrine on the isolated mammalian heart *Anesthesiology* 33 793 1967
- 14 Hardman H. F, Moore J I and Lum B A. B A method for analyzing the effect of pH and the ionization of drugs upon cardiac tissue with special reference to pentobarbital *J Pharmacol Exp Ther* 126 136 1959
- 15 Effendi, H, Versprille A and Wise M E. The negative inotropic effect of barbiturates on the heart of newborn and adult guinea pig *Arch Int Pharmacodyn* 209 127 1973
- 16 Etsten B and Li T H. Hemodynamic changes during thiopental anesthesia in humans: cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume *J Clin Invest* 34 500 1955
- 17 Smith, S L, Webb W M, Sabian L W and Hagaman V D. Cardiac excitability in ether, cyclopropane and halothane anesthesia *Anesthesiology* 23 766 1962.
- 18 Morrow D H, Halsey J V and Logic J R. Anesthesia and digitals VII. The effect of pentobarbital, halothane and methoxyflurane on the A V conduction and inotropic responses to ouabain *Anesth. Analg.* 51 430 1979
- 19 Dresel P E. Cyclopropane-epinephrine cardiac arrhythmias in Price H L and Cohen P J. Effects of anesthetics on the circulation Springfield Illinois, 1964 Charles C Thomas.
- 20 Brodie H B., Boms J J., Morc L C, Lief P A, Burnstein H and Papper E M. The fate of pentobarbital in man and dog and a method for its estimation in biological material *J Pharmacol Exp Ther* 109 76 1953
- 21 Price H L, Kounst P J, Safer J N., Conner H H and Price M L. The uptake of thiopental of body tissues and its relation to the duration of narcosis *Clin Pharmacol Ther* 1 16 1960
- 22 Goldstein A., and Aronow L. The durations of action of thiopental and pentobarbital *J Pharmacol Exp Ther* 128 1 1960
- 23 Guide for the care and use of laboratory animals U S Department of Health Education and Welfare DHEW Pub No (NIH) 73 23 Revised 1972
- 24 Regulations for animal facilities and care Purdue University May 1972
- 25 Babbs C F and Whistler S J. Evaluation of the operating internal resistance, inductance and capacitance of intact damped sine wave defibrillators *Medical Instrumentation* (In press January 1978)



# Comparison of coronary arteriograms with direct measurements of stenosed coronary arteries in dogs\*

Kim P. Gallagher, Ph.D.

John D. Folts, Ph.D.

George G. Rowe, M.D.

*With the technical assistance of Ronald Shebush*

*Madison, Wisconsin*

Selective coronary arteriography is extensively used for evaluation of coronary artery disease. Postmortem studies, however, have suggested that arteriography underestimates the severity of lesions.<sup>1,2</sup> A recent preliminary study utilizing an *in vivo* canine preparation has, on the other hand, suggested that potentially serious overestimations of 15 per cent may occur.<sup>3</sup> In order to assess the accuracy of arteriographic estimates of single, discrete lesions, we have utilized a similar *in vivo* preparation in which partial obstruction of coronary arteries was produced by radiolucent plastic cylinders. The actual amount of stenosis was determined by microscopic examination of silicone rubber casts of the stenotic regions. The physiologic significance of different levels of partial obstruction was determined by measuring the effects of stenoses on phasic coronary blood flow, the reactive hyperemic response, and the pressure gradient across the mechanical obstruction.

From the Cardiology Section, Departments of Medicine and Physiology, University of Wisconsin, Madison, Wisconsin.

This work was supported in part by grants from the National Institute of Health HL 15681 and the Wisconsin Heart Association.

Received for publication July 12, 1977.

Accepted for publication Aug. 19, 1977.

Reprint requests: Kim P. Gallagher, Predoctoral Fellow, Cardiology Section, University of Wisconsin Hospitals, 1300 University Ave., Madison, Wisconsin 53706.

This study was presented in part at the FASEB meeting, April 5, 1977.

## Methods

Sixteen mongrel dogs of either sex weighing between 22.7 kilograms and 34.0 kilograms (average weight, 26.5 kilograms) were premedicated with morphine (3 mg/kg) 30 minutes prior to induction of anesthesia with sodium pentobarbital (30 mg/kg). The animals were intubated and connected to a closed circuit anesthetic machine (Ohio Medical Products) for maintenance with a nitrous oxide-oxygen (75 per cent/25 per cent) mixture of gases.

A left thoracotomy was performed through the fifth intercostal space. The pericardium was incised and the heart suspended in a pericardial cradle. The proximal circumflex coronary artery was dissected free to the first major diagonal branch with ligation of small branches as necessary. An appropriately sized electromagnetic flowprobe (Statham Model SP2202) was placed on the coronary artery to measure coronary blood flow. In 12 of the 16 dogs, electromagnetic flow probes (In Vivo Metric Systems) were placed on the proximal aorta to measure aortic blood flow (Fig. 1).

Aortic blood pressure was measured utilizing a catheter inserted through the femoral artery and connected to a Statham P23Db pressure transducer. Coronary blood pressure was measured with a Khoun Gregg type silicone rubber catheter placed in the circumflex artery distal to the mechanical obstruction and connected to a pres-

sure transducer. Partial obstruction was produced with radiolucent cylinders 3 mm in length machined from physiologically inert plastic (Lexan) with varying internal diameters as shown in the upper right corner of Fig 1. The cylinders are placed on the coronary artery one at a time to produce controlled amounts of stenosis by completely encircling the artery.

A 2.0 silk ligature was passed loosely around the vessel and through plastic tubing and was used to produce temporary complete occlusions for production of reactive hyperemic responses. Epicardial and subendocardial ECG leads were placed in the myocardium supplied by the circumflex artery (Fig 1). All parameters were recorded on a Brush Gould (Model 481) eight channel recorder.

The dog was then transferred to a room equipped for cineangiography and physiologic parameters were allowed to stabilize. Experimental procedures were not initiated until heart rate, blood pressure, coronary blood flow, and aortic flow were steady and unvarying. During the coronary arteriography the animal was ventilated with a Bird Mark VII positive pressure respirator. A Sones coronary arteriographic catheter was passed from the carotid artery into the aorta and then into the circumflex artery under fluoroscopic guidance. Flow and pressure measurements were made before and after the arteriographic catheter was manipulated into the coronary artery. Arteriographic contrast material diatrizoate meglumine and diatrizoate sodium (Renografin 76) was injected manually to visualize the circumflex artery lumen while cineangiograms were taken on 35 mm shellburst film at 60 frames/second. The films were later read to estimate the amount of partial obstruction produced by the plastic cylinders. The arteriograms were magnified (2 times) for inspection and diameters were measured with a millimeter rule. The limit of measuring resolution was set as 0.5 mm and fractions were rounded off to this figure. The arteriographic estimation of cross sectional area was derived by calculation from the diameter measurement assuming a round lumen. Changes in diameter and cross sectional area were expressed as percentage reduction from adjacent unobstructed portions of the vessel.

Pressure and flow measurements were made prior to production of partial obstruction with a plastic cylinder. A cineangiogram was also

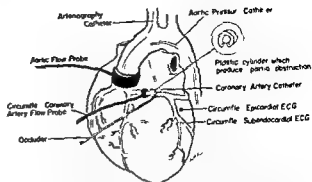


Fig 1 Technique for producing fixed partial obstruction in the left circumflex coronary artery. An electromagnetic flow probe of suitable inside diameter is placed on the vessel. A plastic cylinder 3.0 mm in length, as shown in the upper right corner is selected which will narrow the coronary artery the desired amount and is placed on the vessel. To produce temporary complete occlusions a 2.0 ligature is passed around the vessel and through plastic tubing. The coronary artery catheter is placed through the vessel wall with the tip in the lumen to measure distal coronary artery blood pressure. A cardiac catheter is passed up the femoral artery for aortic blood pressure measurement. Epicardial and subendocardial leads for recording electrograms are placed in the myocardium supplied by the circumflex artery. A Sones coronary catheter is passed down the carotid artery into the aorta and then into the circumflex artery for selective catheterization of the circumflex coronary artery.

obtained during control conditions. At least two temporary (20 second) complete occlusions were performed to observe the normal reactive hyperemic responses in the control state and for all stenoses in order to assess reproducibility of the measurement. A minimum of three minutes was allowed between temporary complete occlusions for the vasculature to recover.

When a cylinder was placed on the coronary artery to produce mechanical stenosis hemodynamic parameters were allowed to stabilize. Approximately 10 minutes after the plastic cylinder was placed on the vessel reactive hyperemic responses were observed and another cineangiogram was obtained. The first cylinder was removed and control measurements of pressures, flows, and reactive hyperemias were repeated. A different level of stenosis was then produced with a second cylinder and the same protocol was followed. If there was sufficient length of the circumflex artery available to permit placing three cylinders on the vessel for casting at necropsy, another level of obstruction was produced with a third cylinder. Visual examination and microscopic measurements indicated

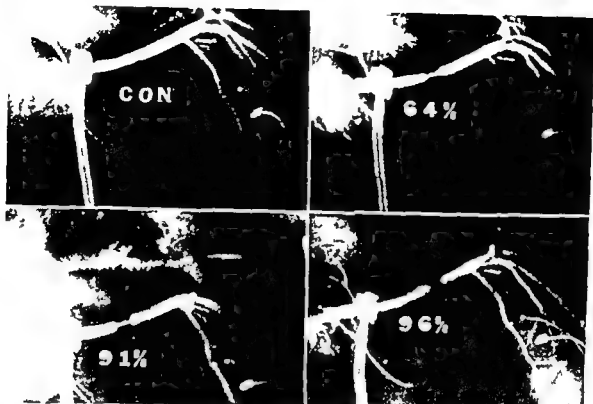


Fig 2 Representative single frame composite of four cineangiographic views from one of the dogs. Coronary cineangiograms were obtained under control unobstructed (CON) conditions and at three levels of obstruction produced in each dog. Because the plastic cylinders are radiolucent the stenotic lumen can be easily visualized. The films were magnified (2 $\times$ ) for measurement of lumen diameter with a millimeter rule. Cross sectional area was obtained by calculation based on the measured diameter. The numbers represent percentage cross sectional area reductions estimated in this manner.

that there was little or no change in external diameter of the vessel up to the first diagonal branch. In 10 of the 16 dogs, three cylinders were used and in six dogs, two cylinders were used.

At the termination of the experiment, the plastic cylinders were replaced on the vessel producing two or three different amounts of stenosis in series. The circumflex artery was cannulated proximally and injected with silicone rubber under physiologic pressure to make a cast of the vessel with the cylinders in place. The vessel was then ligated distally and proximally excised, placed in formalin and later sectioned for direct microscopic measurement of reduced diameter and cross sectional area produced by the cylinders.

At least three sections were made of control (non obstructed) segments and each stenotic segment. The sections were examined under low power microscopy (magnification 25 $\times$ ) and measured with a calibrated grid eyepiece (American Optical Co. Scientific Instruments Div.). The stenosed diameter and cross sectional area measurements were averaged and then compared with control dimensions. Reductions in luminal

diameter and area were expressed as percentages and compared with arteriographic estimates using the microscopic measurements as the standard. Statistical comparisons were made with the paired *t* test using  $p < 0.05$  as the level of significance. The data in the text and figures is presented as mean  $\pm$  standard deviation.

## Results

**Effects of partial obstruction on hemodynamics.** Attention was focused on three levels of partial obstruction: (1) The amount of stenosis which minimally reduced the reactive hyperemic response without creating a pressure gradient; (2) that which produced a measurable pressure gradient across the mechanical obstruction; and (3) the amount of stenosis which nearly abolished reactive hyperemia. A representative record showing the effects of partial obstruction on hemodynamics in one of the dogs is shown in Fig 4.

Data for all of the dogs are summarized in Table I. Unobstructed coronary flow increased to a peak of  $441 \pm 112$  per cent of preocclusion flow after a 20 second complete occlusion. At the first

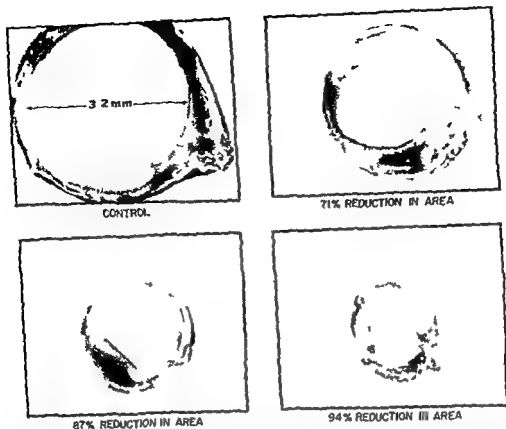


Fig 3 Representative photomicroscopic composite of coronary artery sections from the same dog used in Fig 2. At least three sections of the injected and fixed coronary arteries were obtained from control and stenotic segments. Measurements were averaged and calculated per cent reductions in diameter and cross-section are compared with arteriographic estimates. The numbers represent percentage cross-sectional area reduction based on macroscopic measurements. The lumens of more severely stenosed segments were commonly observed to be irregular as shown in the lower right and left photomicrographs.

level of obstruction there was no measurable difference between mean aortic and mean circumflex blood pressure but the peak reactive hyperemia after a 20 second occlusion was reduced to  $388 \pm 83$  per cent ( $p < 0.001$ ) of preocclusion flow. More severe stenosis producing a small pressure gradient across the stenosis of  $9 \pm 3$  mm Hg (circumflex pressure  $9 \pm 3$  per cent less than simultaneously measured mean arterial blood pressure in the aorta,  $p < 0.01$ ) limited the peak reactive hyperemic response to  $226 \pm 45$  per cent of preocclusion flow ( $p < 0.01$ ). The third level of obstruction nearly abolished reactive hyperemia ( $126 \pm 17$  per cent of preocclusion flow) and produced a pressure gradient of  $32 \pm 11$  mm Hg (circumflex pressure  $35 \pm 12$  per cent less than mean arterial blood pressure measured in the aorta,  $p < 0.01$ ).

The characteristic alteration in phasic pattern with increasing partial obstruction is shown in

Fig 5. We have previously used the diastolic to systolic (D/S) flow ratio as an index of change in coronary blood flow patterns with increasing partial obstruction.<sup>6</sup> The systolic component of flow increases and the diastolic component decreases as the obstruction increases.<sup>7</sup> This is reflected in D/S ratios that approach unity with severe levels of partial obstruction which abolish the hyperemic response to temporary complete occlusion. A decrease in D/S ratios was not always observed at the first level of obstruction which reduced reactive hyperemia by  $25 \pm 8$  per cent. At the two more severe levels of obstruction however a decrease in the D/S ratio was consistently observed (See Table I).

Fig 6 shows the hyperemic effect produced by injecting contrast medium into the circumflex coronary artery during the cineangiogram. There is an initial decrease in coronary blood flow which may be due to the high viscosity of the contrast

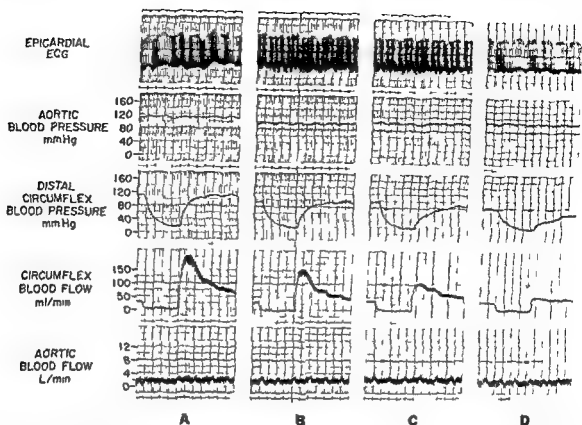


Fig 4 Representative epicardial electrogram, aortic and distal circumflex blood pressure, circumflex and aortic blood flow from one of the dogs recorded as mean values at slow paper speed. Panel A shows the normal reactive hyperemic response to a 20-second complete occlusion before placing a plastic cylinder on the circumflex. Aortic and distal circumflex blood pressure are identical, indicating there is no measurable pressure gradient in the coronary artery due to obstruction by the presence of a flowprobe or the coronary catheter. In panel B is shown the reactive hyperemic response (21 per cent reduced from control) at the first level of obstruction. In panel C the reactive hyperemic response is reduced (64 per cent from control) and there is now a pressure gradient of 7 mm Hg across the mechanical obstruction. The reactive hyperemic response is nearly abolished (90 per cent reduced from control) and a pressure gradient of 26 mm Hg exists at the third level of obstruction shown in panel D.

Table 1 Hemodynamic effects of partial obstruction

|                             | Heart rate<br>(beats/min) | MABP<br>(mm Hg) | MCBP<br>(mm Hg) | $\Delta P$<br>(mm Hg) | CBF<br>(ml/min) | RH<br>maximum<br>(ml/min) | % RH<br>reduction | D/S<br>ratio     |
|-----------------------------|---------------------------|-----------------|-----------------|-----------------------|-----------------|---------------------------|-------------------|------------------|
| Control                     | 126 $\pm$ 33              | 98 $\pm$ 12     | 98 $\pm$ 12     | 0                     | 45 $\pm$ 24     | 166 $\pm$ 78              |                   | 2.51 $\pm$ 0.37  |
| 1st Level of<br>obstruction | 119 $\pm$ 34              | 100 $\pm$ 11    | 100 $\pm$ 11    | 0                     | 44 $\pm$ 24     | 161 $\pm$ 62              | 25 $\pm$ 9 *      | 2.44 $\pm$ 0.36  |
| 2nd Level of<br>obstruction | 129 $\pm$ 32              | 95 $\pm$ 10     | 86 $\pm$ 12     | 9 $\pm$ 3†            | 43 $\pm$ 25     | 95 $\pm$ 88               | 64 $\pm$ 13       | 1.82 $\pm$ 0.30  |
| 3rd Level of<br>obstruction | 130 $\pm$ 39              | 94 $\pm$ 10     | 62 $\pm$ 17     | 32 $\pm$ 11†          | 39 $\pm$ 18     | 49 $\pm$ 27               | 93 $\pm$ 5†       | 1.27 $\pm$ 0.22† |

Abbreviations: MABP = mean arterial blood pressure; MCBP = mean coronary blood pressure (measured distal to mechanical obstruction);  $\Delta P$  = pressure gradient across mechanical obstruction; (MABP-MCBP); CBF = coronary blood flow; RH = reactive hyperemia; D/S ratio = average diastolic CBF/average systolic CBF (measured over ten cardiac cycles).

\*  $p < 0.05$ ; †  $p < 0.01$ ; ‡  $p < 0.001$ .

medium. This is followed by an increase in blood flow which is attenuated by partial obstruction. Contrast medium induced hyperemia was less than the reactive hyperemia produced by a 20 second complete occlusion in the unobstructed

control state and at the first level of obstruction. At the second and third levels of obstruction the contrast medium induced hyperemia and reactive hyperemia were very similar.

Of the 16 dogs only two showed significant

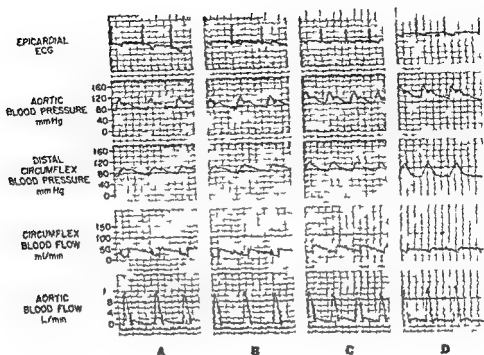


Fig 5 Epicardial electrogram, aortic and distal circumflex blood pressure, circumflex and aortic blood flow from one of the dogs. The phasic flow pattern of normal unobstructed coronary blood flow is shown in panel A, with high flow during diastole and low flow during systole ( $D/S$  ratio = 3.44). In panel B, with obstruction that reduced reactive hyperemia 33 per cent in this dog, the pattern is unaltered ( $D/S$  ratio = 3.22). At the second level of obstruction (panel C), the phasic flow pattern is altered with an increase in the systolic component of flow and decrease in the diastolic component ( $D/S$  ratio = 1.89). With stenosis that reduced reactive hyperemia 95 per cent, the flow pattern is markedly changed ( $D/S$  ratio = 1.04) and a change in the pattern of distal circumflex blood pressure is also observed (panel D).

changes in the reactive hyperemic response after the coronary catheter was manipulated into the circumflex artery. The average change in peak reactive hyperemia in the 14 other dogs after selective catheterization was  $-23$  per cent (NS).

Comparison of coronary arteriograms and microscopic measurements. A  $25 \pm 9$  per cent reduction in peak reactive hyperemia was produced by stenoses estimated as approximately 50 per cent reductions in diameter and 75 per cent reductions in cross-sectional area (Table II). The average differences between diameter and area measurements by the two different methods were statistically nonsignificant.

A  $64 \pm 13$  per cent reduction in peak reactive hyperemia and  $9 \pm 3$  mm Hg gradient were created at the second level of obstruction. Arteriographic measurements overestimated luminal diameter and area a small but significant amount.

The third level of obstruction nearly abolished

the reactive hyperemic response ( $93 \pm 5$  per cent reduction) and produced a pressure gradient of  $32 \pm 11$  mm Hg across the mechanical obstruction. The differences between microscopic and arteriographic measurements of luminal diameter and area again indicated small but highly significant overestimation of lesion severity (See Table II).

### Discussion

Previous investigators assessing the accuracy of arteriographic estimation of stenotic dimensions have examined coronary arteries at autopsy and compared them with antemortem arteriograms.<sup>1</sup> Such data have always been variably suspect because of the time interval between arteriography and postmortem study and the unknown rate of progression or regression of coronary obstruction. In correlative studies comparing human arteriograms made at autopsy and pathological examination of the coronaries, the severity of many coronary lesions was underesti-

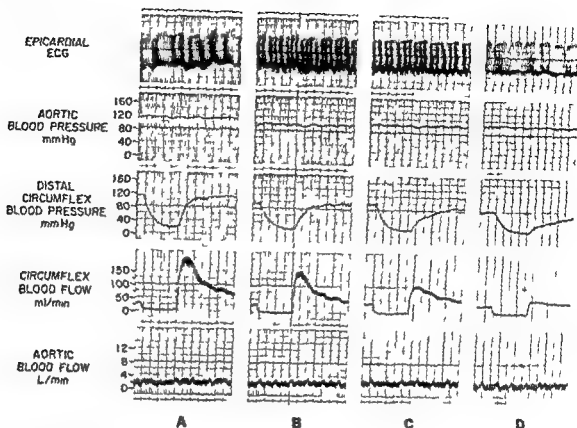


Fig 4 Representative epicardial electrogram aortic and distal circumflex blood pressure circumflex and aortic blood flow from one of the dogs recorded as mean values at slow paper speed. Panel A shows the normal reactive hyperemic response to a 20 second complete occlusion before placing a plastic cylinder on the circumflex. Aortic and distal circumflex blood pressure are identical indicating there is no measurable pressure gradient in the coronary artery due to obstruction by the presence of a flow probe or the coronary catheter. In panel B is shown the reactive hyperemic response (21 per cent reduced from control) at the first level of obstruction. In panel C the reactive hyperemic response is reduced (64 per cent from control) and there is now a pressure gradient of 7 mm Hg across the mechanical obstruction. The reactive hyperemic response is nearly abolished (90 per cent reduced from control) and a pressure gradient of 26 mm Hg exists at the third level of obstruction shown in panel D.

Table 1 Hemodynamic effects of partial obstruction

|                             | Heart rate<br>(beats/min) | MABP<br>(mm Hg) | MCBP<br>(mm Hg) | $\Delta P$<br>(mm Hg) | CBF<br>(ml/min) | RH<br>maximum<br>(ml/min) | % RH<br>reduction | D/S<br>ratio     |
|-----------------------------|---------------------------|-----------------|-----------------|-----------------------|-----------------|---------------------------|-------------------|------------------|
| Control                     | 128 $\pm$ 33              | 98 $\pm$ 12     | 98 $\pm$ 12     | 0                     | 45 $\pm$ 24     | 186 $\pm$ 78              |                   | 2.51 $\pm$ 0.37  |
| 1st Level of<br>obstruction | 119 $\pm$ 34              | 100 $\pm$ 11    | 100 $\pm$ 11    | 0                     | 44 $\pm$ 24     | 161 $\pm$ 62              | 25 $\pm$ 9        | 2.44 $\pm$ 0.36  |
| 2nd Level of<br>obstruction | 129 $\pm$ 32              | 95 $\pm$ 10     | 86 $\pm$ 12     | 9 $\pm$ 3†            | 43 $\pm$ 20     | 90 $\pm$ 58               | 64 $\pm$ 13       | 1.82 $\pm$ 0.30  |
| 3rd Level of<br>obstruction | 130 $\pm$ 39              | 94 $\pm$ 10     | 62 $\pm$ 17     | 32 $\pm$ 11†          | 39 $\pm$ 18     | 49 $\pm$ 27               | 93 $\pm$ 5†       | 1.27 $\pm$ 0.22† |

Abbreviations: MABP = mean arterial blood pressure; MCBP = mean coronary blood pressure (measured distal to mechanical obstruction);  $\Delta P$  = pressure gradient across mechanical obstruction (MABP - MCBP); CBF = coronary blood flow; RH = reactive hyperemia; D/S ratio = average diastolic CBF/average systolic CBF (measured over ten cardiac cycles).

\*  $p < 0.05$ ; †  $p < 0.01$ ; ‡  $p < 0.001$ .

medium. This is followed by an increase in blood flow which is attenuated by partial obstruction. Contrast medium induced hyperemia was less than the reactive hyperemia produced by a 20 second complete occlusion in the unobstructed

control state and at the first level of obstruction. At the second and third levels of obstruction the contrast medium induced hyperemia and reactive hyperemia were very similar.

Of the 16 dogs only two showed significant

intraluminal concentration of contrast medium. In very narrow lesions streaming may occur which could obscure the actual edges of the internal lumen leading to overestimation of lesion severity.

The least severe stenoses were nearly round in conformation whereas more severe stenoses were irregular. The single diameter determined by arteriography depends on the plane viewed since an irregular lesion has several different diameters. Consequently the arteriographic estimate of cross sectional area may be inaccurate. This may explain part of the disparity observed at more severe levels of obstruction.

With more severe stenoses the obstructed region inside the plastic cylinders appeared to progressively change its luminal conformation so that the hemodynamic effects become less severe. Approximately 10 minutes were required for hemodynamic conditions to stabilize after the cylinders were placed on the vessel. Appropriate time therefore was allowed before obtaining reactive hyperemias and cineangiograms. Whether these continued to change slowly between the time of arteriography and histologic section is unknown but it seems unlikely in view of the good agreement obtained.

This study provides an accurate determination of stenosis dimensions plus the hemodynamic effects produced by the partial obstructions. Previous studies have utilized snare devices or pneumatic occluders from which dimension changes were derived from external vessel measurements.<sup>1</sup> With the technique described here internal dimension changes were measured directly with microscopy at necropsy. Because the mass of the vessel wall is not totally compressed with constriction the stenosed vessel wall became thickened relative to control vessel wall width (See Fig 3). In addition the vessel wall was thrown into folds making the internal lumen irregular in shape. It is likely that the irregularity and length (3 mm) of the lesions may closely approximate lesions seen in man. There is a major difference however which should be noted. Many of the lesions seen in man are eccentric as well as irregular while the lumen of the vessel segment inside the plastic cylinder was in the center of the stenotic region. The largest source of error in the estimation of severity of human lesions however arises from the fact that there may be no normal vessel near the area of

Table II Comparison of microscopic measurements with arteriographic estimates of coronary stenoses

|  | % internal area reduction† |        |         |
|--|----------------------------|--------|---------|
|  | A‡                         | M      | Q       |
| 1st level of obstruction‡ (reactive hyperemia reduced)                 | 74 ± 8                     | 73 ± 9 | 15 (NS) |
| 2nd level of obstruction‡ (small pressure gradient across obstruction) | 83 ± 6                     | 86 ± 7 | 36      |
| 3rd level of observation§ (reactive hyperemia abolished)               | 96 ± 3                     | 92 ± 3 | 36      |

Abbreviations: A = arteriographic; M = microscopic; Q = mean difference.

p < 0.05

p < 0.001

†Area measurements were statistically compared with unpaired t tests.

‡There was no significant difference between microscopic and arteriographic measurements at the first level of obstruction. At the second and third level of obstruction arteriography overestimated the extent of area reduction significantly.

§Arteriographic estimates of cross sectional area reduction were obtained by calculation from the diameter estimates made when the films were read.

¶Due to the irregularity of stenoses at the second and third levels of obstruction diameter estimates are not shown. By arteriographic estimation they represent the view through one plane only therefore comparison with microscopic measurements (representing an average value of several different diameters) may not be meaningful.

stenosis and consequently the true baseline from which to estimate stenosis is unknown. Thus if a vessel is uniformly narrowed by 50 per cent no area of stenosis will be identified. In this study in the dog normal vessel before and after the stenosis could easily be identified for comparison.

**Effects of partial obstruction on coronary blood flow.** We have previously demonstrated approximately 10 per cent reduction in peak reactive hyperemia with 36 ± 10 per cent diameter reduction.\* This coincides well with the 25 ± 9 per cent reduction in peak reactive hyperemia observed with 50 per cent ± 10 per cent reduction in diameter. The estimates of stenosis required to produce a pressure gradient or to alter the reactive hyperemic response is similar to previous work from our laboratory and others.<sup>11</sup> The loss of reactive hyperemia is said to be due to full arteriolar dilatation which attempts to compensate for the resistance of the proximal vessel stenosis.<sup>1</sup> Thus the maximally dilated arterioles are unable to respond and no



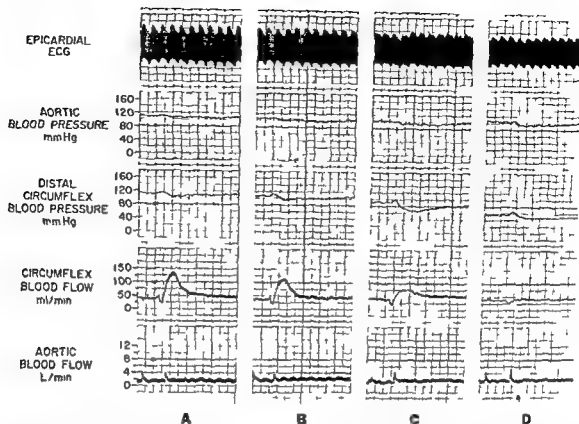


Fig 6 Representative epicardial electrogram aortic and distal circumflex blood pressure circumflex and aortic blood flow from one of the dogs recorded as mean values at slow paper speed. Panel A shows a normal hyperemic response to the administration of Renografin. The average ratio of peak reactive hyperemia to contrast induced hyperemia (RH/CH) for all of the dogs was  $0.73 \pm 0.13$  ( $p < 0.001$ ). With partial obstruction that reduced the reactive hyperemia (panel B) the contrast induced hyperemia was also less than reactive hyperemia (RH/CH ratio  $0.82 \pm 0.14$   $p < 0.01$ ) to ischemic stimuli. At the second (panel C) the third (panel D) levels of obstruction however the contrast induced and reactive hyperemias were more similar (RH/CH ratio  $0.97 \pm 0.15$  NS and  $1.11 \pm 0.15$  NS respectively).

mated by arteriography.<sup>2,3</sup> Pepine and associates<sup>4</sup> also demonstrated variance between arteriographic and direct measurements. Here, we assessed the accuracy of arteriography under more ideal conditions with single discrete, approximately 3 mm lesions and observed good accuracy with slight overestimation of the degree of occlusion produced by severe lesions (greater than 85 per cent cross sectional area reduction).

Because the left chest wall was open through out the experiment there was less interference by chest wall lungs and pericardium to obscure the radiographic view although the right portion of all these structures remained as usual. The arteriographer had an excellent view of each lesion from which to make estimates of dimension reductions, and although the cineangiograms were performed in only one plane (See Fig 2) this was deliberately selected to be optimal.

There was no significant difference between arteriographic estimates and direct microscopic measurements with 50 per cent diameter and 75

per cent area reductions in which peak reactive hyperemia was reduced approximately 25 per cent. At more severe levels of obstruction, however, the difference was significant since arteriography overestimated the severity of lesions. There are several possible reasons to explain this.

The heart was constantly moving up and down with the mechanical respiration required because the dog was thoracotomized. The viewing plane of the rigid fluoroscopic apparatus was therefore always changing slightly. This was compensated to a considerable degree because measurements of the narrowed and normal segments were always made on the same cine frame. Nevertheless some rotation could and did occur. In addition the stenosis may appear more severe because of the reduced contrast blush effects with large amounts of obstruction. Defining the lumen may become more difficult in very narrow regions because as Crawford and colleagues<sup>1</sup> pointed out definition of the lumen depends on the

8. Folts, J D, Kahn D R, Bittar N and Rowe G G Effects of partial obstruction on phasic flow in aortocoronary grafts, *Circulation* 51 and 52 (Suppl. I) 1149 1975
9. Friesinger G C, Schaffer J, Criley J M, Goertner R A and Ross R S Hemodynamic consequences of the injection of radiopaque material, *Circulation* 31 730 1965
10. Crawford D W., Beckenbach, E S, Blankenhorn D H, Selzer R H and Brooks S H Grading of coronary atherosclerosis: Comparison of a modified IAP visual gradient method and a new quantitative angiographic technique *Atherosclerosis* 19 231 1974
11. Krown, E M, Gregg D E and Lowensohn H S Flow in the major branches of the left coronary artery during experimental coronary insufficiency in the unanesthetized dog *Circ Res* 24 99 1968
12. Gould, K L and Lipscomb K Effects of coronary stenoses on coronary flow reserve and resistance *Am J Cardiol* 34 48 1974
13. Klopp E H and Gott V L A simple model of the hemodynamic effects of proximal coronary artery narrowing *Ann Thorac Surg* 19 309 1975
14. Hilla W C and Friesinger G C Reactive hyperemia: An index of the significance of coronary stenoses *Am Heart J* 92 737 1976
15. Elzinga W E and Skinner D Hemodynamic characteristics of initial coronary stenosis in canine coronary arteries *J Thorac Cardiovasc Surg* 69 217 1975
16. Furuse A, Klopp E H, Brawley R K and Gott V L Hemodynamic determinations in the assessment of distal coronary artery disease *J Surg Res* 18 25 1975
17. Gould K L, Lipscomb K and Calvert C Compensatory changes of the distal coronary vascular bed during progressive coronary constriction *Circulation* 51 1085 1975
18. Bache R J, Cobb F R and Greenfield, J C Myocardial blood flow distribution during ischemia induced vasodilation in the unanesthetized dog *J Clin Invest* 54 1467 1974
19. Hess D S and Bache R J Transmural distribution of myocardial blood flow during systole in the awake dog *Circ Res* 38 5 1976
20. Downey J M and Kirk E S Distribution of the coronary blood flow across the canine heart wall during systole *Circ Res* 34 201 1974
21. Mour T W Subendocardial distribution of coronary blood flow and the effect of antianginal drugs *Circ Res* 28 5 1976
22. Ross R S and Friesinger G C Coronary arteriography *Am Heart J* 72 437 1966
23. Rowe G G, Thomsen J H, Stenland R H, McKenna D A, Saler S and Corliss W J A study of hemodynamics and coronary blood flow in man with coronary artery disease *Circulation* 39 139 1969

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material."

post occlusion increase in flow is observed. It could be that when the stenosis in the proximal coronary artery reaches a degree of severity which will permit only resting coronary flow, the arteriolar resistance becomes unimportant and no longer controls flow even though the arterioles are not dilated fully.

There is a characteristic alteration in the phasic pattern of coronary blood flow with increasing partial obstruction. As coronary narrowing becomes more severe, the systolic fraction of flow increases and the diastolic fraction decreases. Thus the diastolic-systolic flow ratio approaches 1.0 from the control value of  $2.51 \pm 0.37$  in unobstructed coronary arteries (Table I). With severe stenoses there is a large pressure gradient across the proximal obstruction. Also distal coronary pulse pressure increases, perhaps due to the low diastolic resistance offered by dilated arterioles. A low diastolic coronary blood pressure could explain the redistribution of flow away from the endocardial muscle layers observed by other investigators, because endocardial flow occurs primarily in diastole<sup>10</sup> and pressure may be inadequate to drive sufficient blood flow through the inner layers.<sup>1</sup>

Less severe coronary stenoses, however, are also potentially dangerous. The significance of lesions less than 70 per cent (diameter reduction) is the partial loss of myocardial vasodilator reserve that may jeopardize the heart when blood flow demand is increased and may produce symptoms.<sup>7</sup> For example, with proximal coronary constriction (if it is assumed that the full proximal coronary lumen is required for maximal flow) during exercise, some point must be reached when coronary vasodilation is inadequate to permit blood flow to meet myocardial demands. The blood flow/demand ratio will decrease until ischemia results.<sup>2</sup>

### Summary

An anesthetized, open chest dog preparation was used to assess the accuracy of arteriography in determining the dimensions of experimentally produced coronary stenoses while monitoring the hemodynamic effects of the lesions. Partial obstruction was produced with radiolucent plastic cylinders 3 mm in length made with varying internal diameters. Cineangiographic estimates of per cent stenosis were compared with microscopic

measurements of silicone rubber casts of the obstructed coronary arteries. Three levels of partial obstruction were examined which produced measurable physiologic change.

1 Mechanical reduction of coronary luminal diameter of  $50 \pm 10$  per cent and cross sectional area  $73 \pm 9$  per cent (arteriographic estimates  $51 \pm 7$  per cent and  $74 \pm 8$  per cent) produced no pressure gradient but reduced the reactive hyperemic response  $25 \pm 9$  per cent.

2 Reduction in diameter of  $61 \pm 10$  per cent and cross sectional area  $86 \pm 7$  per cent (arteriographic estimates  $69 \pm 9$  per cent and  $89 \pm 6$  per cent) produced a pressure gradient of  $11 \pm 3$  mm Hg and reduced reactive hyperemia  $64 \pm 13$  per cent.

3 Reduction in diameter of  $71 \pm 4$  per cent and cross sectional area  $92 \pm 3$  per cent (arteriographic estimates  $80 \pm 6$  per cent and  $96 \pm 3$  per cent) produced a pressure gradient of  $32 \pm 11$  mm Hg and reduced the reactive hyperemia  $93 \pm 5$  per cent.

There was no significant difference between arteriographic and microscopic measurements at the first level of obstruction which reduced reactive hyperemia 25 per cent. The differences at the two higher levels of obstruction, however, were significant. The arteriographic estimates appeared to overestimate the severity of lesions that reduced cross sectional area 85 per cent or more.

### REFERENCES

- 1 Vlodaver Z, Frech R, Van Tassel R A and Edwards J E. Correlation of the antemortem coronary arteriogram and the postmortem specimen. *Circulation* 47: 169, 1973.
- 2 Eusterman J H, Achter R W P, Kincaid O W and Brown A L. Atherosclerotic disease of the coronary arteries. A pathologic-radiologic correlative study. *Circulation* 26: 1288, 1962.
- 3 Gary C R, Hoffman H A, Hammond W S, Miller K L and Oseasohn R O. Correlation of arteriographic and pathologic findings in the coronary arteries in man. *Circulation* 25: 494, 1962.
- 4 Pepine C, Feldman R, and Conti R. An unrecognized, potentially serious limitation of coronary angiography. *Circulation* 54 (Suppl II): 162, 1976.
- 5 Abouni E M, Gregg D E and McGranahan C M. Regression and reappearance of coronary collaterals. *Am J Physiol* 220: 66, 1971.
- 6 Folts J D, Gallagher K and Rowe G G. Hemodynamic effects of controlled degrees of coronary artery stenosis in short term and long term studies in dogs. *J Thorac Cardiovasc Surg* 73: 722, 1977.
- 7 Folts J D, Gallagher K P and Rowe G G. Ischaemic coronary blood flow changes with partial coronary obstruction. *Physiologist* 17: 223, 1974.

- 8 Folts, J D Kahn H R Bitar N and Rowe G G Effects of partial obstruction on phase flow in aortocoronary grafts, *Circulation* 51 and 52 (Suppl. 1) 1148 1975
- 9 Friesinger G C Schaffer J Orley J M Goertner R A and Ross R S Hemodynamic consequences of the injection of radioopaque material *Circulation* 31 730 1965
- 10 Crawford D W Beckenbach E S Blankenhorn D H Seltzer R H and Brooks E H Grading of coronary atherosclerosis Comparison of a modified IAP visual gradient method and a new quantitative angiographic technique, *Atherosclerosis* 19 231 1974
- 11 Khouri, E M Gregg D F and Lowensohn H S Flow in the major branches of the left coronary artery during experimental coronary insufficiency in the unanesthetized dog *Circ Res* 23 99 1968
- 12 Gould K L and Lipscomb K Effects of coronary stenoses on coronary flow reserve and resistance *Am J Cardiol* 34 45 1974
- 13 Klopp E H and Gott V L A simple model of the hemodynamic effects of proximal coronary artery narrowing *Ann Thorac Surg* 19 309 1975
- 14 Hilla W S and Friesinger G C Reactive hyperemia An index of the significance of coronary stenoses *Am Heart J* 92 737 1976
- 15 Elzinga W E and Skinner D E Hemodynamic characteristics of initial coronary stenosis in canine coronary arteries *J Thorac Cardiovasc Surg* 69 217 1975
- 16 Furuse A Klopp E H Brawley H K and Gott V L Hemodynamic determinations in the assessment of distal coronary artery disease *J Surg Res* 19 75 1975
- 17 Gould K L Lipscomb K and Calvert C Compensatory changes of the distal coronary vascular bed during progressive coronary constriction *Circulation* 51 1085 1975
- 18 Bache R J Cobb F R and Greenfield J C Myocardial blood flow distribution during ischemia induced vasodilation in the unanesthetized dog *J Clin Invest* 54 1467 1974
- 19 Hesa D S and Bache R J Transmural distribution of myocardial blood flow during systole in the awake dog *Circ Res* 38 5 1976
- 20 Downey J M and Kirk E S Distribution of the coronary blood flow across the canine heart wall during systole *Circ Res* 34 251 1974
- 21 Mour T W Subendocardial distribution of coronary blood flow and the effect of antianginal drugs *Circ Res* 28 5 1970
- 22 Ross R S and Friesinger G C Coronary arteriography *Am Heart J* 72 437 1966
- 23 Rowe G G Thomsen J H Stenland R R McHenna H A Sialer S and Corliss R J A study of hemodynamics and coronary blood flow in man with coronary artery disease *Circulation* 39 139 1969

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material."

# The incidence and significance of contraction bands in endomyocardial biopsies from normal human hearts\*

Gerald E. Adomian Ph.D.  
Michael M. Laks M.D.  
M. E. Billingham M.D.  
Torrance and Stanford Calif

With increasing use of myocardial biopsy as a diagnostic tool, different criteria of pathology have evolved from tissues obtained from biopsy and postmortem specimens. We previously reported that contraction bands may be produced artifactually by the biopsy procedure in the fresh, but not the postmortem or perfused fixed normal rat and dog hearts.<sup>1</sup> Contraction bands have been used as a morphological index of pathology in conditions such as ischemia, cardiomyopathy, and catecholamine toxicity. Therefore, the aim of this study was to determine the incidence of contraction bands in biopsies from the normal human heart.

## Method

Endomyocardial biopsy samples were obtained from the right ventricle of 12 normal young human transplant donors by means of the Stanford-Caves-Schultz biptome and fixed immediately in 2 1/2 per cent glutaraldehyde buffered in

0.1 M sodium cacodylate to pH 7.4 and 10 per cent buffered formalin.

**Preparation of tissue for paraffin section study by light microscopy.** The biopsy tissue fixed in formalin was dehydrated, infiltrated, and embedded in paraffin. Six micron thick sections were stained with hematoxylin-eosin and Masson's trichrome stain.

**Preparation of tissue for plastic section study by light and electron microscopy.** The glutaraldehyde fixed tissue was subsequently rinsed in 0.1 M sodium cacodylate buffer then post-fixed in buffered 1 per cent osmium tetroxide. After dehydration in graded concentrations of alcohol and propylene oxide, the tissue was embedded in Epon 812 and polymerized overnight at 60° C. Samples were sectioned for light and electron microscopy. One micron thick sections for light microscopy were stained with toluidine blue or with methylene blue-azure II. One thousand Å thin sections for electron microscopy were stained in a saturated aqueous uranyl acetate solution for 60 minutes and in lead citrate for four minutes.

**Method for quantitation of the number of contraction bands.** All quantitative studies were performed utilizing a 63x planapochromat oil immersion objective lens (NA 1.4) of a Zeiss Universal research microscope. To quantitate the light microscopic observations, the following previously devised grading system for the number of contraction bands was utilized: 0 (absent), 1 (mild), 2 (moderate), and 3 (severe), which represented 0 to 5, 6 to 10, and 11 or more cells with contraction bands per sq. mm of tissue respectively.<sup>2</sup>

From the Division of Cardiology, Harbor General Hospital, UCLA School of Medicine, Torrance, Calif., and the Department of Pathology, Stanford University Medical School, Stanford, Calif.

This work has been done during the tenure of an American Heart Association Greater Los Angeles Affiliate Grant in Aid No. 507 C1, a National Institute of Health Grant No. H11471-03A1 CVB, and in part by a National Institute of Health Grant No. H113108-07 (Clinical Cardiac Transplantation).

Received for publication July 26, 1977.

Accepted for publication Sept. 6, 1977.

Reprint requests to Gerald E. Adomian, M.D., Division of Cardiology, Harbor General Hospital, 1000 W. Carson Street, Torrance, Calif. 90509.

A portion of this study was presented to the American Section of the International Society for Heart Research, May 1977, in Pasadena, California.

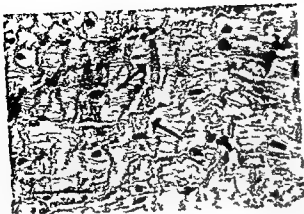


Fig 1 Light micrograph of a paraffin section from a normal human right ventricle. Note the extensive degree of contraction band formation (arrows) (Masson's trichrome stain. Bar equals 50 microns)

### Results

With hematoxylin-eosin staining of paraffin sections contraction bands appeared eosinophilic whereas with Masson's trichrome staining the bands were easily recognized because of their staining a brilliant red (Fig 1). In plastic sections observed with light microscopy contraction bands were interspersed between the normal cross striations within the myofibril and frequently extended transversely across the entire myofiber (Figs 2 and 3). These contraction bands were present juxtaposed to the intercalated discs and the nuclei as well as between these structures. A spectrum of sarcomere lengths existed in which the normal interval between Z lines were reduced to the point at which several intervals merge into one dense homogeneous contraction band. With electron microscopy the myofilaments appeared to be arranged haphazardly within the hypercontracted regions which appeared densely eosinophilic (Fig 4).

Contraction bands were observed in biopsy samples from 11 out of 12 hearts and from 10 out of 10 hearts in the Epon and paraffin embedded tissues respectively (Table I). Although the morphology of contraction bands and the definition of cell boundaries were more distinct in plastic than paraffin embedded tissue the latter was adequate for the technique of the quantitation method utilized. In the plastic embedded sections nine hearts demonstrated a severe (3rd) degree of contraction band formation whereas one heart showed a moderate (2nd) degree one heart a mild (1st) degree and one heart a zero degree of contraction band formation (Table I).



Fig 2 Light micrograph of a 1 micron thick Epon section from a normal human right ventricle. Note the presence of a severe degree of contraction band formation (arrows). Intercalated disc (arrowhead) (Methylene blue—azure II Bar equals 50 microns)

In the paraffin embedded sections nine hearts demonstrated a severe (3rd) degree and one heart a mild (1st) degree of contraction band formation. Tissue samples from two hearts were not obtained (Table I).

### Discussion

Hypercontraction of sarcomeres below their normal minimal length, approximately 1.5 microns, results in the appearance of clumped masses of sarcoplasm which have been called contraction bands. Contraction bands have been referred to as dense bodies, dense bands, eosinophilic banding, contractures, contraction clumps, and cytoplasmic banding.<sup>1,2</sup> We consider that these contraction bands are caused by excessive interdigitation and folding of the myofilaments. Since contraction bands have been present in myocardial tissue associated with various cardiac pathological states, their presence has been interpreted as being a part of these pathological processes. However, in concert with this study of myocardial tissue taken from human hearts is the previous report of myocardial biopsies obtained from completely normal rat and dog hearts which showed a severe degree of contraction band formation.<sup>1,2</sup> Therefore the following important question is evoked: Is the presence of contraction bands in myocardial tissue a result of a pathological condition or an artifact of technique? This



Fig 3 High magnification light micrograph of the same Epon section of normal heart as seen in Fig 2. Note the detail within the contraction bands (arrow) Intercalated discs (arrowhead) (Bar equals 25 microns)

Table 1 The incidence of contraction band formation in biopsy samples obtained from normal human hearts

| Donor | Degree of contraction band formation |                   |
|-------|--------------------------------------|-------------------|
|       | Epon sections                        | Paraffin sections |
| 1     | 3                                    | 3                 |
| 2     | 1                                    | —                 |
| 3     | 3                                    | 3                 |
| 4     | 3                                    | 3                 |
| 5     | 3                                    | 3                 |
| 6     | 0                                    | 3                 |
| 7     | 3                                    | 1                 |
| 8     | 3                                    | 3                 |
| 9     | 3                                    | —                 |
| 10    | 2                                    | 3                 |
| 11    | 3                                    | 3                 |
| 12    | 3                                    | 3                 |

question is partially answered by the previous study in which contraction bands were not seen in the myocardial tissue taken from the same normal animals after a postmortem period of 40 minutes. Of further importance even though the endocardial biopsy samples were taken rapidly contraction bands were not seen in hearts perfused with a high concentration of potassium or fixative. Consequently we may conclude in general that contraction bands seen in the heart



Fig 4 Electron micrograph from a normal human ventricle. Note the transition zone (bottom of figure) of normal sarcomere lengths merging into an irreversible dense contraction band. Also note the disarray of the myofilaments (arrow) within the contraction bands (Uranyl acetate and lead citrate Bar equals 1 micron)

tissue obtained from postmortem tissue or from biopsied tissue obtained after the perfusion of the coronary arteries with high concentrations of potassium or fixative are to be considered due to the pathological condition and not the result of an artifact of preparation. On the other hand contraction bands present in tissues obtained from endocardial biopsies may have been produced artifactually; however the possibility that a pathological state may also exist in this myocardial tissue cannot be ruled out.

What is the genesis of these artifactually produced contraction bands in normal hearts? From the previous study of myocardial tissue obtained under various conditions in lower animals the infusion of fixative into the coronary arteries did not produce contraction bands; consequently fixative alone applied to the endocardial biopsy specimen itself is not responsible for contraction band formation. Since the inhibition of membrane depolarization with the infusion of high concentration of potassium prevented the formation of contraction bands we may conclude that the mechanical aspect of the biopsy procedure does not directly activate the contractile machinery. From these results the following

hypotheses were developed for the mechanism of contraction band formation. The formation of contraction bands are due to the depolarization of the myocardial cell by the biopsy procedure resulting in activation of the contractile apparatus together with sarcomeres capable of hypercontraction because their shortening is unopposed.

The results of the present study utilizing normal human hearts demonstrates as in the previous animal study that contraction bands cannot be relied upon as an index of pathology in tissues obtained during biopsy. However contraction bands may be considered a morphological index of pathology in myocardial tissue obtained 4/3 minutes postmortem.

### Summary

With increasing use of myocardial biopsy as a diagnostic tool different criteria of pathology have evolved from tissues obtained from biopsy and postmortem specimens. We reported that contraction bands may be produced artifactually by the biopsy procedure in the fresh but not the postmortem or perfused fixed normal rat and dog hearts. Contraction bands have been used as a morphological index of pathology. From 12 normal human transplant donors endomyocardial biopsy samples were obtained from the right ventricle were fixed immediately and then processed for light and electron microscopy. Contraction bands were quantitated by assigning 0, 1, 2, and 3 to represent 0-1 to 5, 6 to 10, and 11 or more cells per square millimeter with contrac-

tion bands. A large number of contraction bands were present in 11 out of 12 hearts. 3rd, 2nd, 1st and zero degrees of contraction bands were present in 11, 0, 1 and 0 samples respectively. We conclude that contraction bands may be produced artifactually in normally human hearts and based upon the rat and dog study that the determinants of contraction band formation are activation of the contractile machinery by the biopsy procedure together with sarcomeres capable of hypercontraction because their shortening is unopposed.

Furthermore contraction bands may be considered a morphological index of pathology in tissue obtained postmortem and after perfusion fixation but not in tissue obtained from biopsies.

The authors wish to acknowledge the technical assistance of Marilyn Masek, Bob Heusser, and A. Richard Soto.

### REFERENCES

1. Adomian G E, Lake M, Garner D and Swan H J C. The determinants for the production of contraction bands in normal rats and dogs. *Fed Proc* 35:229, 1976.
2. Adomian G E, Lake M M and Swan H J C. The significance of contraction band formation in normal hearts. *Thirty fourth Annual Proceedings of the Electron Microscopy Society of America* 1976 pp 312-313.
3. Reichenbach D D and Benditt E P. Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. *Hum Pathol* 1:12, 1970.
4. Sonnenblick E H. Correlation of myocardial ultrastructure and function. *Circulation* 38:29, 1968.
5. Cullen M J and Fulthorpe J J. Stages in fiber breakdown in Duchenne muscular dystrophy. *An EM study*. *J Neurol Sci* 24:179, 1975.





Fig 3 High magnification light micrograph of the same Epon section of normal heart as seen in Fig 2. Note the detail within the contraction bands (arrow). Intercalated discs (arrowhead). (Bar equals 25 microns)

Table I The incidence of contraction band formation in biopsy samples obtained from normal human hearts

| Donor | Degree of contraction band formation |                   |
|-------|--------------------------------------|-------------------|
|       | Epon sections                        | Paraffin sections |
| 1     | 3                                    | 3                 |
| 2     | 1                                    | —                 |
| 3     | 3                                    | 3                 |
| 4     | 3                                    | 3                 |
| 5     | 3                                    | 3                 |
| 6     | 0                                    | 3                 |
| 7     | 3                                    | 1                 |
| 8     | 3                                    | 3                 |
| 9     | 3                                    | —                 |
| 10    | 2                                    | 3                 |
| 11    | 3                                    | 3                 |
| 12    | 3                                    | 3                 |

question is partially answered by the previous study in which contraction bands were not seen in the myocardial tissue taken from the same normal animals after a postmortem period of 40 minutes. Of further importance, even though the endocardial biopsy samples were taken rapidly contraction bands were not seen in hearts perfused with a high concentration of potassium or fixative. Consequently, we may conclude in general that contraction bands seen in the heart



Fig 4 Electron micrograph from a normal human ventricle. Note the transition zone (bottom of figure) of normal sarcomere lengths merging into an irreversible dense contraction band. Also note the disarray of the myofilaments (arrow) within the contraction bands (Uranyl acetate and lead citrate). Bar equal 1 micron.

tissue obtained from postmortem tissue or from biopsied tissue obtained after the perfusion of the coronary arteries with high concentrations of potassium or fixative are to be considered due to the pathological condition and not the result of an artifact of preparation. On the other hand, contraction bands present in tissues obtained from endocardial biopsies may have been produced artifactually; however, the possibility that a pathological state may also exist in this myocardial tissue cannot be ruled out.

What is the genesis of these artifactually produced contraction bands in normal hearts? From the previous study of myocardial tissue obtained under various conditions in lower animals, the infusion of fixative into the coronary arteries did not produce contraction bands; consequently, fixative alone applied to the endocardial biopsy specimen itself is not responsible for contraction band formation. Since the inhibition of membrane depolarization with the infusion of high concentration of potassium prevented the formation of contraction bands, we may conclude that the mechanical aspect of the biopsy procedure does not directly activate the contractile machinery. From these results, the following

hypotheses were developed for the mechanism of contraction band formation. The formation of contraction bands are due to the depolarization of the myocardial cell by the biopsy procedure resulting in activation of the contractile apparatus together with sarcomeres capable of hypercontraction because their shortening is unopposed.

The results of the present study utilizing normal human hearts demonstrates, as in the previous animal study, that contraction bands cannot be relied upon as an index of pathology in tissues obtained during biopsy. However, contraction bands may be considered a morphological index of pathology in myocardial tissue obtained 40 minutes postmortem.

### Summary

With increasing use of myocardial biopsy as a diagnostic tool, different criteria of pathology have evolved from tissues obtained from biopsy and postmortem specimens. We reported that contraction bands may be produced artifactually by the biopsy procedure in the fresh but not the postmortem or perfused fixed normal rat and dog hearts. Contraction bands have been used as a morphological index of pathology. From 12 normal human transplant donors, endomyocardial biopsy samples were obtained from the right ventricle, were fixed immediately and then processed for light and electron microscopy. Contraction bands were quantitated by assigning 0, 1, 2, and 3 to represent 0 to 5, 6 to 10, and 11 or more cells per square millimeter with contrac-

tion bands. A large number of contraction bands were present in 11 out of 12 hearts; 3rd, 2nd, 1st, and zero degrees of contraction bands were present in 11, 0, 1, and 0 samples respectively. We conclude that contraction bands may be produced artifactually in normally human hearts and based upon the rat and dog study that the determinants of contraction band formation are activation of the contractile machinery by the biopsy procedure together with sarcomeres capable of hypercontraction because their shortening is unopposed.

Furthermore, contraction bands may be considered a morphological index of pathology in tissue obtained postmortem and after perfusion fixation but not in tissue obtained from biopsies.

The authors wish to acknowledge the technical assistance of Marilyn Masek, Bob Heusser, and A. Richard Soto.

### REFERENCES

1. Adomian G E, Laks M, Garner D., and Swan H J C. The determinants for the production of contraction bands in normal rats and dogs. *Fed Proc* 35:279, 1976.
2. Adomian G E, Laks M M, and Swan H J C. The significance of contraction band formation in normal hearts. Thirty-fourth Annual Proceedings of the Electron Microscopy Society of America, 1976, pp 312-313.
3. Reichenbach D D and Benditt E P. Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. *Hum Pathol* 1:125-130.
4. Sonnenblick E H. Correlation of myocardial ultrastructure and function. *Circulation* 38:29, 1968.
5. Cullen M J and Fulthorpe J J. Stages in fiber breakdown in Duchenne muscular dystrophy. *An EM study*. *J Neurol Sci* 24:179, 1975.

# Creatine phosphokinase MB isoenzyme in hypothermia Case reports and experimental studies

C Jeffrey Carlson, MD \*

Blanka Emilson

Elliot Rapaport, MD

*With the technical assistance of Mr Leshe Bible  
San Francisco Calif*

The determination of the total activity of serum creatine phosphokinase (CPK) and its use as a specific test for acute myocardial damage is well recognized.<sup>1</sup> However, since total serum CPK activity can be elevated by other conditions,<sup>2</sup> the appearance in serum of the MB isoenzyme of CPK (CPK MB) has been proposed as a more specific indicator of acute myocardial infarction.<sup>3,4</sup> The occurrence of greater than 2 per cent of the MB isoenzyme of CPK has been reported to be in the serum of patients with muscular dystrophy,<sup>5</sup> muscular inflammatory disorders,<sup>6</sup> ischemic rhabdomyolysis with myoglobinuria,<sup>7</sup> carbon monoxide poisoning,<sup>8</sup> malignant hyperthermia,<sup>9</sup> Reye's syndrome,<sup>10</sup> and in certain cases of minor cardiac trauma.<sup>10</sup> However, these conditions are clinically distinct from acute myocardial infarction, and there is usually little difficulty in distinguishing among them.

Six critically ill patients with profound hypothermia are reported in whom the CPK MB

isoenzyme was detected without other clinical or postmortem evidence of myocardial infarction. To investigate the possible source and pattern of CPK appearance in serum, we studied the effects of similar levels of hypothermia in mongrel dogs.

## Materials and methods

Twenty mongrel dogs weighing from 13.5 to 20.6 kilograms were studied. The dogs were anesthetized with intravenous pentobarbital, 25 mg/Kg body weight intubated and ventilated on a Harvard ventilator for 24 hours. Periodic additional intravenous doses of pentobarbital were required to maintain anesthesia. Central body temperature was monitored with a thermistor placed high in the rectum. The electrocardiogram was monitored on a DR 12 Electronics for Medicine optical recorder. Dogs which required drugs to control severe sinus bradycardia or cardioversion for ventricular fibrillation were excluded from the study. All animals were killed at the end of the period of anesthesia.

In seven dogs after induction of anesthesia and control blood sampling, serial blood samples were drawn at 1 to 2 hour intervals for 24 hours for determination of total CPK activity. In four of the dogs deep hypothermia (23 to 25° C) was induced by total body cooling with externally applied ice bags; the duration of hypothermia was limited to 6 hours. The subsequent rate of rewarming was controlled by a heating pad. In

From the Cardiology Unit of the Medical Service, San Francisco General Hospital Medical Center and the Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco.

Supported by United States Public Health Service Program Project Grant HL-06785.

Received for publication Aug 12 1977.

Accepted for publication Sept 30 1977.

Reprint requests to: Elliot Rapaport, MD, Cardiopulmonary Unit 5G, 1 San Francisco General Hospital, Medical Center, 1001 Potrero Ave, San Francisco, Calif 94110.

Supported by Cardiovascular Research Institute Training Grant HL-05351.

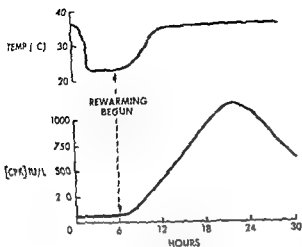


Fig 1 Body temperature and total serum CPK activity in a dog subjected to 6 hours of deep hypothermia

the remaining three dogs anesthesia was continued for 24 hours with the animals maintained at normal body temperature

In 13 dogs a midline sternotomy was performed. Control biopsy specimens were obtained from the anterolateral wall of the left ventricle and from striated muscle from two locations in the cervical paraspinal musculature. After 22 hours of anesthesia biopsy specimens were again obtained from adjacent myocardial and striated muscle areas. In seven of these dogs deep hypothermia was induced as just described and similarly maintained for 6 hours. In the remaining six dogs normal body temperature was maintained for the duration of anesthesia.

Serum samples from experimental animals and from patients were analyzed for total CPK activity by the Rosalki method. Results were expressed in IU/L at 25°C. Creatine phosphokinase isoenzyme analysis was performed by electrophoretic separation and fluorescent scanning according to the method of Elefitch.<sup>8</sup> Results were expressed in per cent of the total scanned area of MM, MB and BB isoenzyme.

Biopsied samples (100 mg of wet tissue from left ventricle and striated muscle) were homogenized in the cold by mortar and pestle in 1000  $\mu$ L of 0.1 mole/L using tris hydrochloride buffer containing 0.01 mole/L cysteine at pH 8.0. The resulting homogenate was spun at 3000 rpm for 20 minutes. The supernatant was analyzed for total CPK activity as noted previously.<sup>1</sup> The unspun homogenate was analyzed for total

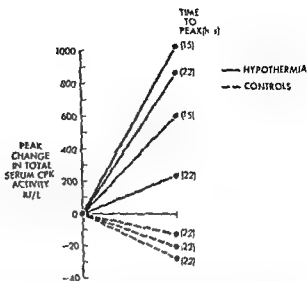


Fig 2 Peak observed changes in serum CPK activity in seven anesthetized dogs followed for 24 hours. Four dogs (solid lines) were subjected to an initial 6-hour period of hypothermia (23 to 24°C). The remaining three dogs (broken lines) were maintained at normal body temperatures.

protein concentration by the Biuret method. A 40 ml sample was diluted with 2.8 ml of Biuret solution and allowed to stand for 30 minutes at 25°C. The specimen was read at 540 nm on a Gilford DU spectrophotometer with no filter. Readings were compared with a standard albumin curve (bovine fraction V, New England Reagent Laboratory) and the results are expressed in mg/L total protein. At least three separate samples of homogenate were analyzed. Creatine phosphokinase activity per mg of protein was obtained by dividing the total CPK concentration by the total protein concentration. All experimental specimens were analyzed within 2 hours after sampling.

## Results

Fig 1 shows the typical serum pattern of CPK activity observed in one of the hypothermic dogs. Similar results were observed in the other three dogs. Increased CPK activity was noted after rewarming was begun but before normothermia was reached, attaining a maximum 15 to 22 hours after hypothermia was initiated. In the three normothermic control dogs observed for 24 hours total serum CPK activity actually fell (Fig 2). No serum CPK MB isoenzyme activity was noted in any dog.

After hypothermia, both heart and striated

# Creatine phosphokinase MB isoenzyme in hypothermia Case reports and experimental studies

C Jeffrey Carlson, M D \*

Blanka Emillon

Elliot Rapaport, M D

*With the technical assistance of Mr Leslie Bible*

*San Francisco Calif*

The determination of the total activity of serum creatine phosphokinase (CPK) and its use as a specific test for acute myocardial damage is well recognized.<sup>1</sup> However, since total serum CPK activity can be elevated by other conditions,<sup>2</sup> the appearance in serum of the MB isoenzyme of CPK (CPK MB) has been proposed as a more specific indicator of acute myocardial infarction.<sup>3,4</sup> The occurrence of greater than 2 per cent of the MB isoenzyme of CPK has been reported to be in the serum of patients with muscular dystrophy,<sup>5</sup> muscular inflammatory disorders,<sup>6</sup> ischemic rhabdomyolysis with myoglobinuria,<sup>7</sup> carbon monoxide poisoning,<sup>8</sup> malignant hyperthermia,<sup>9</sup> Reye's syndrome,<sup>10</sup> and in certain cases of minor cardiac trauma.<sup>11</sup> However, these conditions are clinically distinct from acute myocardial infarction, and there is usually little difficulty in distinguishing among them.

Six critically ill patients with profound hypothermia are reported in whom the CPK MB

From the Cardiology Unit of the Medical Service, San Francisco General Hospital Medical Center and the Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco.

Supported by United States Public Health Service Program Project Grant HL-06785.

Received for publication Aug 12 1977

Accepted for publication Sept 30 1977

Reprint requests to Elliot Rapaport, M D, Cardiopulmonary Unit 5 G, 1 San Francisco General Hospital, Medical Center, 1001 Potrero Ave, San Francisco, Calif 94110.

Supported by Cardiovascular Research Institute Training Grant HL-03511.

isoenzyme was detected without other clinical or postmortem evidence of myocardial infarction. To investigate the possible source and pattern of CPK appearance in serum, we studied the effects of similar levels of hypothermia in mongrel dogs.

## Materials and methods

Twenty mongrel dogs weighing from 13.5 to 20.6 kilograms were studied. The dogs were anesthetized with intravenous pentobarbital 25 mg/Kg body weight, intubated, and ventilated on a Harvard ventilator for 24 hours. Periodic additional intravenous doses of pentobarbital were required to maintain anesthesia. Central body temperature was monitored with a thermistor placed high in the rectum. The electrocardiogram was monitored on a DR 12 Electronics for Medicine optical recorder. Dogs which required drugs to control severe sinus bradycardia or cardioversion for ventricular fibrillation were excluded from the study. All animals were killed at the end of the period of anesthesia.

In seven dogs after induction of anesthesia and control blood sampling, serial blood samples were drawn at 1 to 2 hour intervals for 24 hours for determination of total CPK activity. In four of the dogs, deep hypothermia (23 to 25°C) was induced by total body cooling with externally applied ice bags; the duration of hypothermia was limited to 6 hours. The subsequent rate of rewarming was controlled by a heating pad. In

medical management but over the ensuing 3 weeks repeated bouts of sepsis occurred and the patient died of *Pseudomonas* pneumonia. During this period the previously low QRS and T voltage resolved and there was no change to suggest myocardial infarction.

At postmortem examination the gallbladder was obstructed by a large stone. The heart had a normal configuration without a pericardial effusion. Moderate coronary atherosclerosis was present with narrowing up to 50 per cent. There were no thrombi and no microscopic or gross evidence of myocardial infarction.

**Case No 5** A 65-year-old unconscious woman was admitted to San Francisco General Hospital Medical Center on December 11, 1975. She was lethargic with multiple bruises over the face, arms and trunk. Blood pressure was unobtainable, pulse was 50 beats/minute, respiration 20 breaths/minute and rectal temperature 23.3°C. The patient had neurologic evidence of left carotid occlusion involving the left hemisphere and hypothalamus. Other than marked kyphoscoliosis and evidence of dehydration, the remainder of the examination was negative. Hemoglobin was 13.8 Gm/100 ml and the white blood cell count was within the normal range. Arterial blood pH was 7.47,  $P_{CO_2}$  27 mm Hg and  $P_{O_2}$  50 mm Hg. Blood glucose was 177 mg/100 ml, blood urea nitrogen 168 mg/100 ml, sodium 145 mEq/L, potassium 3.4 mEq/L, chloride 104 mEq/L, and carbon dioxide 13 mEq/L. The chest roentgenogram showed no abnormalities. The electrocardiogram showed sinus bradycardia with an elevated J junction consistent with hypothermia. The SGOT level was 230 IU/L and LDH 360 IU/L with LDH (45 per cent) greater than LDH (16 per cent). Total CPK was 76 IU/L with 12 per cent MB and 4 per cent BB isoenzyme. No myoglobin was found in serum or urine. Over the ensuing 36 hours the hemodynamic and pulmonary status deteriorated and the patient died.

Postmortem examination revealed calcified coronary arteries and luminal narrowings of 50 per cent. There was however no gross or microscopic evidence of coronary occlusion or myocardial infarction.

**Case No 6** A 91-year-old unresponsive woman was admitted to San Francisco General Hospital Medical Center on February 9, 1976. She was lethargic, cachectic and dehydrated and had no evidence of trauma. Blood pressure was 140/0 mm Hg, pulse 96 beats/minute, respiration 30 breaths/minute and rectal temperature 33.8°C. There was evidence of bilateral pneumonia, a right pleural effusion, and abdominal distention. There were no localizing neurologic findings. Hemoglobin was 11.2 Gm/100 ml and white blood cell count 8,000/ $\mu$ L with a marked shift to the left. Urine was clear with a negative benzidine test. Blood urea nitrogen was 71 mg/100 ml, sodium 130 mEq/L, potassium 5.0 mEq/L, chloride 113 mEq/L, and carbon dioxide 11 mEq/L. Arterial blood pH was 7.33,  $P_{CO_2}$  29 mm Hg and  $P_{O_2}$  53 mm Hg. Serum amylase was 118 U/L, SGOT was 140 IU/L and LDH 4.5 IU/L. Serial enzyme determinations are shown in Table III. The electrocardiogram showed normal sinus rhythm and nonspecific ST and T wave changes. Intravenous infusion of fluids, antibiotics and steroids was started. Renal, hemodynamic, intestinal and mental status improved over the next 40 days and the patient was transferred to a chronic care facility. Serial electrocardiograms failed to show any evidence of myocardial infarction.

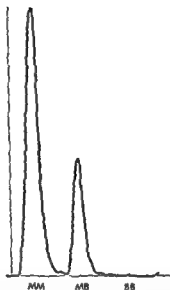


Fig 3 Creatine phosphokinase (CPK) isoenzyme electrophoresis and fluorescence scan from Case No 5. The total CPK activity was 1015 IU/L. The area under the MB isoenzyme portion of the scan was 27 per cent of the total area.

## Discussion

The presence in serum of CPK MB isoenzyme activity has been shown to be a sensitive and specific indicator of ischemic myocardial injury.<sup>2</sup> In addition it has been suggested that serial measurement of CPK MB isoenzyme activity may indicate not only the presence but also the extent of myocardial infarction.<sup>3,4</sup> Therefore it is important to document the clinical circumstances in which CPK MB isoenzyme appears in serum, particularly those situations that can be confused clinically with acute myocardial infarction. All the patients described in this report presented with serious medical problems, problems which may be associated with or result from acute myocardial infarction. Two of the six patients presented with cerebrovascular accidents. Case No 3 presented with respiratory acidosis. Case No 6 had marked serum amylase elevation, initially suggesting bowel infarction or pancreatitis. Case No 4 had evidence of profound hypoglycemia and sepsis. There was no evidence of myoglobinuria in any patient. The only common factor among these patients was the presence of profound hypothermia.

Of the three patients who died, all showed varying degrees of coronary atherosclerosis but no gross or microscopic evidence of acute occlusion or myocardial infarction. Of the survivors

Table I Tissue CPK changes in experimental hypothermia induced in dogs

| Tissue          | Mean total CPK activity<br>(IU/mg protein $\pm$ 1 SD)<br>After 24 hours of anesthesia |   |   |
|-----------------|---|---|---|
|                 | All control dogs<br>(n = 13)  | Under normo thermic conditions<br>(n = 6) | After an initial 6 hours of hypothermia<br>(23 to 24° C)<br>(n = 7) |
| Left ventricle  | 152 $\pm$ 45  | 158 $\pm$ 63                              | 118 $\pm$ 44*   |
| Striated muscle | 220 $\pm$ 56  | 229 $\pm$ 48                              | 165 $\pm$ 46†   |

\* P < 0.02 paired Student's t test (value versus control)

† P < 0.01 paired Student's t test (value versus control) and unpaired (value versus mean of anesthesia group)

muscle specimens showed an average reduction of 21 per cent in CPK activity from the initial value (Table I) in both cases. No reduction in CPK activity from either heart or striated muscle was observed in the open chest preparations subjected to anesthesia alone (Table I).

### Case reports (Table II)

**Case No. 1** An 85 year old comatose woman was admitted to San Francisco General Hospital Medical Center on December 5, 1975. On admission the rectal temperature was 35.6° C, pulse 50 beats/minute, blood pressure 160/0 mm Hg and respiration 30 breaths/minute. Physical findings were consistent with a mid brain or intracerebral cerebrovascular accident. Laboratory studies were as follows: hematocrit 44 per cent, white blood cell count 9400/ $\mu$ L, arterial blood pH 7.45, Pco<sub>2</sub> 26 mm Hg, sodium 127 mEq/L, and potassium 3.1 mEq/L. Urine was clear with 3+ glucose and a negative benzidine test. Chest roentgenograms showed a right upper lobe infiltrate. The electrocardiogram showed complete left bundle branch block and atrial fibrillation with a ventricular rate of 50 to 70 beats/minute with no change from a tracing taken 9 months previously. Total serum CPK in sample obtained on admission was 131 IU/L with 5 per cent MB and trace BB isoenzymes.

Despite supportive medical care the patient died 14 hours after admission. Postmortem examination revealed an acute right intracerebral hemorrhage with mid brain herniation. The coronary arteries showed moderate atherosclerosis without occlusive disease. Gross and microscopic heart examination showed no evidence of recent or old myocardial infarction.

**Case No. 2** An 83-year old comatose woman was admitted to San Francisco General Hospital Medical Center on October 28, 1975. On admission the rectal temperature was 22.2° C, heart rate 30 beats/minute, blood pressure 90/0 mm Hg and respiration 16 breaths/minute. She appeared emaciated and severely dehydrated with diffusely increased muscle tone and

had an early sacral decubitus ulcer. A lumbar puncture showed low cerebrospinal fluid pressure only. The hematocrit was 32 per cent with a white blood cell count of 9700/ $\mu$ L. Arterial blood pH was 7.36, Pco<sub>2</sub> 34 mm Hg, Po<sub>2</sub> 104 mm Hg while breathing 100 per cent oxygen. Blood urea nitrogen was 52 mg/100 ml, sodium 142 mEq/L, potassium 2.3 mEq/L, and glucose 365 mg/100 ml. The urine was clear with a 1+ positive benzidine test and 5 to 10 red blood cells per high power field. The chest roentgenogram showed no abnormalities. The electrocardiogram showed sinus bradycardia, QT = 0.6 seconds and left ventricular hypertrophy. The patient gradually responded to medical treatment with resolution of coma, hypothermia, dehydration and normalization of blood potassium and glucose levels. The urine remained clear with no evidence of myoglobin. Serial electrocardiograms showed resolution of QT prolongation and no evidence of myocardial infarction. Serum enzyme data are summarized in Table III. The CPK isoenzyme pattern on the second day after admission is shown in Fig. 3. The patient was transferred 16 days after admission to a convalescent hospital.

**Case No. 3** A 24 year old comatose man without spontaneous respiration after an overdose of barbiturates was admitted to San Francisco General Hospital Medical Center on December 2, 1975. The rectal temperature was 34.4° C, blood pressure 142/88 mm Hg, pulse 84 beats/minute and respiration 20 breaths/minute after intubation. Physical examination revealed no other abnormalities. Hemoglobin was 15.6 Gm/100 ml and white blood cell count 11,700/ $\mu$ L. While being maintained on 100 per cent oxygen arterial blood pH was 6.90, Pco<sub>2</sub> 88 mm Hg and Po<sub>2</sub> 250 mm Hg. Hypercarbia resolved promptly after intubation. The urine was clear with a negative benzidine test. The roentgenogram showed no abnormalities. The electrocardiogram showed normal sinus rhythm, right bundle branch block, QT prolongation and nonspecific ST-T wave changes. The serum CPK was 227 IU/L with 4 per cent MB isoenzyme. On the day after admission there was still 3 per cent MB isoenzyme with a total CPK of 282 IU/L. Serum glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH) remained within normal limits. The coma gradually resolved and the patient was extubated and finally discharged after 5 days. Serial electrocardiograms showed resolution of QT prolongation but no evolutionary changes to suggest an acute myocardial infarction. The patient had no history of prior cardiac disease and there was no family history of premature coronary disease.

**Case No. 4** A 68 year old unresponsive man who was a chronic alcoholic was admitted to San Francisco General Hospital Medical Center on November 22, 1975. The patient was emaciated and had a rectal temperature of 31.6° C, blood pressure of 80/60 mm Hg, pulse 100 beats/minute and respiration 20 breaths/minute. There was no evidence of trauma. Except for moderate hepatomegaly no other physical abnormalities were apparent. Hemoglobin was 11.2 Gm/100 ml and white blood cell count was 21,900/ $\mu$ L. Arterial pH was 7.49, Pco<sub>2</sub> 34 mm Hg and Po<sub>2</sub> 65 mm Hg. The urine was clear with 2 red blood cells per high power field and 1+ positive benzidine test. Blood glucose was 15 mg/100 ml. Serial enzymes are shown in Table III. The chest roentgenograms showed no abnormalities. The electrocardiogram showed atrial fibrillation at a rate of 100 beats/minute and low QRS and T wave voltage. The patient responded initially to

medical management but over the ensuing 3 weeks repeated bouts of sepsis occurred and the patient died of *Pseudomonas* pneumonia. During this period the previously low QRS and T voltage resolved and there was no change to suggest myocardial infarction.

At postmortem examination the gallbladder was obstructed by a large stone. The heart had a normal configuration without a pericardial effusion. Moderate coronary atherosclerosis was present with narrowing up to 50 per cent. There were no thrombi and no microscopic or gross evidence of myocardial infarction.

Case No. 5 A 65-year-old unconscious woman was admitted to San Francisco General Hospital Medical Center on December 15, 1975. She was lethargic with multiple bruises over the face, arms and trunk. Blood pressure was unobtainable, pulse was 50 beats/minute, respiration 20 breaths/minute and rectal temperature 33.3 °C. The patient had neurologic evidence of left carotid occlusion involving the left hemisphere and hypothalamus. Other than marked kyphoscoliosis and evidence of dehydration the remainder of the examination was negative. Hemoglobin was 13.8 Gm/100 ml, and the white blood cell count was within the normal range. Arterial blood pH was 7.47,  $P_{CO_2}$  27 mm Hg and  $P_{O_2}$  50 mm Hg. Blood glucose was 177 mg/100 ml, blood urea nitrogen 168 mg/100 ml, sodium 146 mEq/L, potassium 3.4 mEq/L, chloride 104 mEq/L, and carbon dioxide 13 mEq/L. The chest roentgenogram showed no abnormalities. The electrocardiogram showed sinus bradycardia with an elevated J function consistent with hypothermia. The SCOT level was 30 IU/L, and LDH 365 IU/L with LDH (25 per cent) greater than LDH (16 per cent). Total CPK was 76 IU/L with 12 per cent MB and 4 per cent BB isoenzyme. No myoglobin was found in serum or urine. Over the ensuing 36 hours the hemodynamic and pulmonary status deteriorated and the patient died.

Postmortem examination revealed calcified coronary arteries and luminal narrowings of 50 per cent. There was however no gross or microscopic evidence of coronary occlusion or myocardial infarction.

Case No. 6 A 91-year-old unresponsive woman was admitted to San Francisco General Hospital Medical Center on February 9, 1976. She was lethargic, cachectic and dehydrated and had no evidence of trauma. Blood pressure was 140/80 mm Hg, pulse 96 beats/minute, respiration 30 breaths/minute and rectal temperature 33.8 °C. There was evidence of bilateral pneumonia, a right pleural effusion and abdominal ileus. There were no localizing neurologic findings. Hemoglobin was 11.2 Gm/100 ml and white blood cell count 8,000/L with a marked shift to the left. Urine was clear with a negative benzidine test. Blood urea nitrogen was 71 mg/100 ml, sodium 150 mEq/L, potassium 5.0 mEq/L, chloride 113 mEq/L, and carbon dioxide 11 mEq/L. Arterial blood pH was 7.33,  $P_{CO_2}$  29 mm Hg, and  $P_{O_2}$  53 mm Hg. Serum amylase was 11.8 U/L, SGOT was 140 IU/L, and LDH 455 IU/L. Serial enzyme determinations are shown in Table III. The electrocardiogram showed normal sinus rhythm and nonspecific ST and T wave changes. Intravenous infusion of fluids, antibiotics and steroids was started. Renal hemodynamic, intestinal and mental status improved over the next 20 days and the patient was transferred to a chronic care facility. Serial electrocardiograms failed to show any evidence of myocardial infarction.

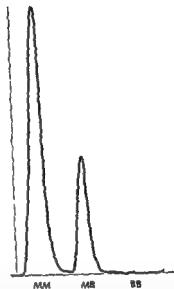


Fig. 3. Creatine phosphokinase (CPK) isoenzyme electrophoresis and fluorescence scan from Case No. 5. The total CPK activity was 1015 IU/L. The area under the MB isoenzyme portion of the scan was 27 per cent of the total area.

## Discussion

The presence in serum of CPK MB isoenzyme activity has been shown to be a sensitive and specific indicator of ischemic myocardial injury.<sup>2</sup> In addition it has been suggested that serial measurement of CPK MB isoenzyme activity may indicate not only the presence but also the extent of myocardial infarction.<sup>1, 13</sup> Therefore it is important to document the clinical circumstances in which CPK MB isoenzyme appears in serum, particularly those situations that can be confused clinically with acute myocardial infarction. All the patients described in this report presented with serious medical problems, problems which may be associated with or result from acute myocardial infarction. Two of the six patients presented with cerebrovascular accidents. Case No. 3 presented with respiratory acidosis. Case No. 5 had marked serum amylase elevations initially suggesting bowel infarction or pancreatitis. Case No. 4 had evidence of profound hypoglycemia and sepsis. There was no evidence of myoglobinuria in any patient. The only common factor among these patients was the presence of profound hypothermia.

Of the three patients who died all showed varying degrees of coronary atherosclerosis but no gross or microscopic evidence of acute occlusion or myocardial infarction. Of the survivors



Table II Summary of patient data

| Patient No | Age (yr) | Sex | Admitting diagnosis      | Admitting rectal temp (° C) | Maximum observed values |                    |                    |                  | % MB      | Outcome                       |
|------------|----------|-----|--------------------------|-----------------------------|-------------------------|--------------------|--------------------|------------------|-----------|-------------------------------|
|            |          |     |                          |                             | Total LDH (IU/L)        | % LDH <sub>1</sub> | % LDH <sub>2</sub> | Total CPK (IU/L) |           |                               |
| 1          | 85       | F   | Cerebrovascular accident | 25.6                        | —                       | —                  | —                  | 131              | 5         | Died 14 hours after admission |
| 2          | 83       | F   | Accidental hypothermia   | 22.2                        | 495                     | 37                 | 42                 | 1884             | 32        | Discharged                    |
| 3          | 24       | M   | Drug overdose            | 34.4                        | —                       | —                  | —                  | 227              | 4         | Discharged                    |
| 4          | 68       | M   | Hypoglycemia and sepsis  | 31.6                        | 385                     | —                  | —                  | 428              | 7         | Died 21 days after admission  |
| 5          | 65       | F   | Cerebrovascular accident | 23.3                        | 365                     | 16                 | 25                 | 76               | 12        | Died 36 hours after admission |
| 6          | 91       | F   | Dehydration              | 33.8                        | 433                     | 23                 | 27                 | 805              | (4% BB) 4 | Discharged                    |

Table III Serum enzyme data obtained during hospital course of patients

| Patient and parameter | Day 1 | Day 2 | Day 3    | Day 4 | Day 5    | Day 7    |
|-----------------------|-------|-------|----------|-------|----------|----------|
| <b>Patient No. 2</b>  |       |       |          |       |          |          |
| Temperature (° C)     | 22.2  | 35.5  | 36.7     | 37.0  | 36.7     | 36.7     |
| Total CPK (IU/L)      | 1884  | 1015  | 1250     | 381   | 164      | 122      |
| % MB                  | 32    | 27    | Not done | 7     | 3        | Not done |
| LDH (IU/L)            | 365   | 381   | Not done | 495   | Not done | 475      |
| % LDH <sub>1</sub>    | 36    | 40    | Not done | 37    | Not done | 52       |
| % LDH <sub>2</sub>    | 41    | 43    | Not done | 42    | Not done | 40       |
| <b>Patient No. 4</b>  |       |       |          |       |          |          |
| Temperature (° C)     | 31.6  | 34.6  | 35.3     | —     | 36.8     | —        |
| Total CPK (IU/L)      | 428   | 287   | 124      | —     | 58       | —        |
| % MB                  | 7     | 6     | 4        | —     | Trace    | —        |
| LDH (IU/L)            | 285   | 395   | 355      | —     | 323      | —        |
| <b>Patient No. 6</b>  |       |       |          |       |          |          |
| Temperature (° C)     | 33.8  | 36.3  | 37.2     | —     | —        | —        |
| Total CPK (IU/L)      | 805   | 648   | 399      | —     | —        | —        |
| % MB                  | 4     | 10    | 4        | —     | —        | —        |
| LDH (IU/L)            | 356   | 433   | 520      | —     | —        | —        |
| % LDH <sub>1</sub>    | 20    | 23    | —        | —     | —        | —        |
| % LDH <sub>2</sub>    | 26    | 27    | —        | —     | —        | —        |

CPK = creatine phosphokinase LDH = lactic dehydrogenase

there was inadequate clinical evidence to establish the presence of a discrete acute myocardial infarction. Case No. 3 was young without any personal or family history of premature heart disease and had no electrocardiographic evidence of infarction. Despite the advanced age of the two remaining patients (Cases No. 2 and 5) and the severity of their underlying medical problems there was no electrocardiographic evidence of infarction, no evidence of congestive heart failure to suggest pump dysfunction, and no evidence of an abnormal LDH isoenzyme pattern.

We undertook a series of experiments in dogs to determine whether or not these clinical observa-

tions could be reproduced under controlled conditions. In these experiments, dogs made hypothermic for only 2 hours showed a consistent rise in total serum CPK activity. This increase in enzyme activity occurred during the period of rewarming before body temperature had returned to normal and rose to a peak 15 to 22 hours after hypothermia was begun. In the control experiments after 24 hours of anesthesia under normothermic conditions serum CPK actually decreased. This may reflect the effects of decreased muscle activity analogous to that observed in hospitalized patients on bed rest.<sup>11</sup>

In the animal experiments the changes

observed in total enzyme activity were solely the result of increased CPK MM isoenzyme activity. The CPK MB isoenzyme was not observed in any animal serum sample. This is to be expected since CPK MB isoenzyme makes up a much smaller fraction of total myocardial CPK activity in dogs than it does in man.<sup>15</sup>

Because we did not observe changes in serum CPK MB isoenzyme activity in these animal studies, it might be difficult to comment on the source of this isoenzyme in the patients. However, data from the open chest animal studies indicate that the increase in total serum CPK activity due to hypothermia results from a 21 per cent reduction in total CPK activity in both striated and myocardial muscle. The peak total serum CPK activities observed in the closed chest studies are lower than would be expected for such massive cellular CPK release—a finding similar to that observed in myocardial infarction. The reason for this discrepancy was not specifically investigated but must be due to either increased local enzyme catabolism or decreased enzyme synthesis due to hypothermia. Regardless, these findings in the dog studies indicate that the changes in total CPK activity observed in the patients with hypothermia probably reflect enzyme release from both striated and myocardial muscle cells.

In addition, the source of the serum CPK MB isoenzyme observed in the hypothermic patients was probably myocardial cellular release. We believe that this conclusion is justified if we can extrapolate our findings of a reduced total myocardial CPK activity owing to hypothermia from dogs to man. Because the MB isoenzyme makes up a larger fraction of total myocardial CPK activity in man than in dogs, any reduction in total cardiac cellular enzyme activity in man may be associated with the appearance of this isoenzyme in serum. The level of CPK MB observed also supports a cardiac origin for the isoenzyme. We noted that the MB isoenzyme constituted 4 to 27 per cent of total CPK activity in man; the only tissue that contains greater than 4 per cent MB isoenzymes is the myocardium.

How the changes that we observed in myocardial CPK activity relate to actual irreversible myocardial damage is not entirely clear. Hjekshus and Sobel showed that depression of myocardial CPK activity is a useful indicator of the extent of irreversible tissue damage. However, histochemical studies performed in rats with

ischemic injury induced by isoproterenol demonstrated a marked early reduction of cellular CPK activity followed by a gradual return of enzyme activity to almost normal levels after 4 hours.<sup>1</sup> In that study, only the subendocardium underwent necrosis without recovery of CPK activity. However, methods were not used to determine if the cytoplasmic protein with CPK activity was actually lost from reversibly damaged cells or if enzyme activity was inhibited locally with no contribution to serum enzyme activity changes. Consequently, we cannot know with certainty whether the increased serum total CPK and CPK MB isoenzyme activities observed in hypothermia represent a loss of enzyme activity from irreversibly damaged cells or a transient phenomenon related to reversible muscle injury. In either case, the appearance of the CPK MB isoenzyme in the serum of patients with profound hypothermia does not necessarily indicate the occurrence of the discrete acute myocardial infarction. Alternatively, in the absence of other clinical criteria of infarction, the presence of the MB isoenzyme of CPK in serum of patients with hypothermia probably indicates participation of myocardium in a diffuse ischemic process. This process may occur either during hypothermia with local enzyme sequestration and release during rewarming or during rewarming itself. The animal data would support either view.

### Summary

Six patients with severe medical disorders and profound hypothermia are presented who had elevated total serum creatine phosphokinase (CPK) and CPK MB isoenzyme activity without clinical or postmortem evidence of acute myocardial infarction. Experiments in dogs indicate that hypothermia reduces total CPK activity in both striated and myocardial muscle, resulting in increased serum enzyme activity. These data suggest that profound hypothermia may result in diffuse striated and cardiac muscle cellular injury without evidence of discrete infarction with consequent release of CPK MB isoenzyme into serum.

### REFERENCES

1. Vincent W R and Rapaport E. Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. *Am. J. Cardiol.* 15:17, 1965.
2. Nevins, M A, Saran M, Bright M and Lyon L J.

- Pitfalls in interpreting serum creatine phosphokinase activity JAMA 224 1382 1973
- 3 Kontinen A and Somer H Determination of serum creatine kinase isoenzymes in myocardial infarction Am J Cardiol 29 817 1972
- 4 Klein M S Shell W E and Sobel H E Serum creatine phosphokinase (CPK) isoenzymes after intra muscular injections surgery and myocardial infarction Cardiovasc Res 7 412 1973
- 5 Somer H Donner M Murros J and Kontinen A A serum isozyme study in muscular dystrophy Particular reference to creatine kinase aspartate aminotransferase and lactic acid dehydrogenase isozymes Arch Neurol 29 343 1973
- 6 Brownlow K and Elevitch F R Serum creatine phosphokinase isoenzyme (CPK<sub>2</sub>) in myositis A report of six cases JAMA 230 1141 1974
- 7 Russell M M Bleiweis S Brownlow K and Elevitch F R Ischemic rhabdomyolysis and creatine phosphokinase isoenzymes A diagnostic pitfall JAMA 235 632 1976
- 8 Ando V Conn R B Mangoli H F and Ando G Diagnostic efficacy of myocardial creatine phosphokinase using polyacrylamide disk gel electrophoresis Am J Clin Pathol 61 599 1974
- 9 Rock R C Dreskin R Kickler T, and Winsatt T Creatine kinase isoenzymes in serum of patients with Reye's syndrome Clin Chim Acta 62 159 1975
- 10 Tonkun A M Lester R M Guthrow C E, Roe C R, Hackel D B and Wagner G S Persistence of MB isoenzyme of creatine phosphokinase in the serum after minor iatrogenic cardiac trauma Absence of postmortem evidence of myocardial infarction Circulation 51 62 1975
- 11 Rosalki S H An improved procedure for serum creatine phosphokinase determination J Lab Clin Med 69 69 1967
- 12 Elevitch F R Fluorometric techniques in clinical chemistry Boston 1973 Little Brown & Company p 244
- 13 Sobel H E and Shell W E Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction Progr Cardiol 4 165 1975
- 14 Sobel H E Bresnahan G F Shell W E and Yoder H D Estimation of infarct size in man and its relation to prognosis Circulation 46 640 1972
- 15 Roberts R Gowda A S Ludbrook P A, and Sobel H E Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction Am J Cardiol 36 433 1975
- 16 Kjekshus J K and Sobel H E Depressed myocardial creatine phosphokinase activity following experimental myocardial infarction in rabbit Circ Res 27 403, 1970
- 17 Babs N Kim S and Farrell E C Histochemistry of creatine phosphokinase J Mol Cell Cardiol 8 599 1976

### Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition however, that the copier pay the stated per copy fee through the Copyright Clearance Center Inc P O Box 765 Schenectady, N Y 12301 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works, or for resale.

## The prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis

Charles D Johnson MD  
F Martínez Catínchi MD  
Río Piedras Puerto Rico

The classical electrocardiographic features of hypokalemia have been extensively studied and are presently quite well known. However, there appears to be less familiarity with the role of hypokalemia alone in the causation of cardiac arrhythmias: atrioventricular (AV) and intraventricular conduction disturbances (IVCD). Arrhythmias include sinus bradycardia, supraventricular and ventricular premature contractions in bigeminal form with short coupling intervals, atrial flutter, atrial tachycardia with block, atrioventricular dissociation (AVD), ventricular tachycardia (VT) and fibrillation and sudden death.

The existence and frequency of AV and IVCD in hypokalemia continues to be controversial. First degree and second degree Wenckebach AV block have occasionally been observed.<sup>1</sup> Chung<sup>2</sup> believes that clinical AV block other than a prolonged P-R interval is rare and an IVCD is extremely unusual. Fowler<sup>3</sup> notes that ordinarily hypokalemia produces little or no change in the P-R and QRS intervals. Fisch<sup>4</sup> states in recent reviews that in contrast with experimental hypokalemia, prolongation of the P-R interval in the clinical setting is rare and that examination of large numbers of electrocardiograms (ECGs) of patients with low serum potassium (K) by numerous investigators reveals

no statistically significant prolongation of the P-R and QRS intervals. Noteworthy moderate widening and bizarreness of the QRS complex has only rarely been observed in pure severe hypokalemia.<sup>5</sup> This communication depicts prominent electrocardiographic features of severe hypokalemia observed in a Negro male presenting with hypokalemic periodic paralysis (HPP).

### Case report

This 37-year-old Negro Puerto Rican male enjoyed good health until 1974 when he had an episode of transient paraparesis. He recovered spontaneously and was well for the following two years except for myalgias that appeared after strenuous exercise. On April 22, 1976 he engaged in unusually heavy labor and in the evening he ate a large amount of cake and ice cream. On the following day he awoke with weakness of the legs and was taken to another hospital where cerebrospinal fluid analysis was normal. An infusion of 5 per cent dextrose in water (D/W) was started. There was progression of symptoms as judged by the development of flaccid quadriplegia and dysphagia with retention of secretions and difficult breathing. He was then transferred to our hospital. The remainder of the history and family history were negative. On admission April 24 the physical examination was normal except for an irregular pulse of 96 and absent deep tendon reflexes. He was immediately intubated and assisted ventilation was started. The 6 AM serum potassium was 1.3 mEq/L, while serum sodium, chloride and CO<sub>2</sub> content were normal. Blood gas determinations revealed the following: PO<sub>2</sub> = 63 mm Hg, pCO<sub>2</sub> = 21 mm Hg, HCO<sub>3</sub><sup>-</sup> = 11.5 mEq/L and pH = 7.37. 743 these are at variance with the CO<sub>2</sub> content value. Spontaneously eight hours later the patient could move all extremities and the ECG and serum electrolytes had reverted to normal. Potassium administration was begun twelve hours after admission when the results of the initial electrolytes became available. Unfortunately the patient received some 4 liters of D/W or dextrose in normal saline during the first 24 hours. Subsequent studies showed a normal hemogram, urinalysis, blood chemistry profile, serum electro-

From the University of Puerto Rico School of Medicine, Río Piedras, Puerto Rico.

Received for publication November 22, 1976.

Accepted for publication February 19, 1977.

Reprint requests: Charles D. Johnson, MD, Department of Medicine, University of Puerto Rico School of Medicine, Río Piedras, Puerto Rico 00931.

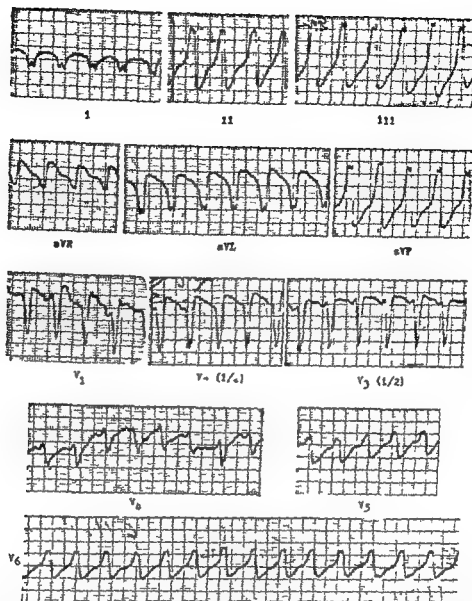


Fig 1 ECG 4 24 76 3 A M Rate = 120 P R interval = 0.11 0.12 sec QRS interval = 0.20 sec (total 0.40 sec) QT (QU) interval = 0.40 sec axis + 110 degrees Probable sinus tachycardia All complexes are nondescript but the QRS complexes are extremely wide. The ST segments are depressed in Leads II III aVR V<sub>1</sub> and elevated in Leads I aVL aV<sub>L</sub> V<sub>2</sub> The T and U waves are not identified See text

lytes chest roentgenogram esophagram bariatric enema sigmoidoscopy electroencephalogram electromyogram nerve conduction velocity serum aldolase pulmonary function studies serum thyroxine and cortisol and 24 hour urine studies for 17 hydroxy and ketosteroids sodium potassium bicarbonate and creatinine clearance The serum and urinary aldosterone values while on a regular diet were normal The sodium and potassium content of muscle after recovery were 71.6 and 62.1 mEq/L respectively these represent an increase of muscle sodium and a marked decrease of muscle potassium Light and electron microscopy revealed minimal atrophic changes increased glycogen granules and mitochondria and vacuolizations within muscle fibers immunofluorescent examination showed faint linear staining with IgG along the interstitial spaces all consistent with periodic paralysis The patient was discharged on a low salt low carbohydrate diet and acetazolamide 250 mg twice daily

Interpretation of the electrocardiograms The ECG's were all taken during the same day (within 16-1/4 hours of each other) (See legends to illustrations) Fig 1 tracing was

obtained in the Emergency Room on arrival Unfortunately no serum potassium was drawn to correspond to this interesting ECG when it was most likely lower than 1.3 mEq/L All the electrocardiographic complexes were nondescript the QRS complexes were markedly widened (at least 0.20 sec) the ST segments were either depressed or elevated but neither junction J nor T and U waves could be delineated If the small rounded waves preceding the QRS complexes in Lead V<sub>1</sub> are indeed P waves there is apparently shortening of the P R interval and an early QRS in the last complex (cut off) of this strip VT or accelerated idioventricular rhythm are considered less likely

Fig 2 ECG's were taken 3 hours later when the serum potassium was 1.3 mEq/L. Notable changes have transpired in that the QRS complexes have narrowed to 0.10 sec duration and the ST segments T U and P waves are now identifiable The ST segments are depressed in many leads U waves are prominent and are somewhat fused to the T waves. The first beat in Lead III is probably a junctional escape beat (JFB) with aberration This tracing 2A is suggestive of the

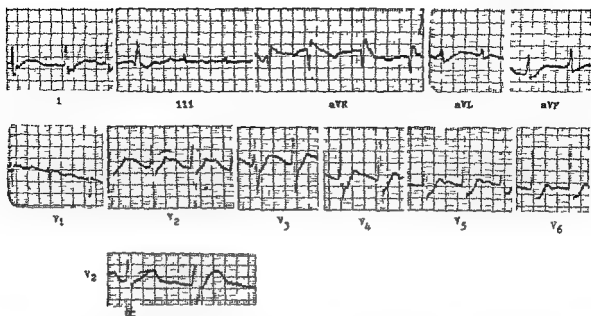


Fig 2A ECG 6 AM QRS interval = 0.10 sec QT = 0.40 sec QU = 0.54 sec axis + 45 degrees Depressed ST segments in Leads I II aVL aVF V1 V2 V3 V4 V5 V6 and elevated in aVL U waves are prominent The T and U waves appear to be fused but are sufficiently separated in the precordial leads to be identified. The lower V lead shows a P wave separated from the fused TU waves

usual hypokalemia pattern Fig 2B however reveals striking complex alterations in AV conduction Atypical Type 1 second-degree Wenckebach AV block develops which appears to be unlike variations previously described In strip a of Fig 2B the P R interval of the second Wenckebach group increases in the third and fourth beats and then remains the same (0.24 sec) The P R of the first beat of the last group does not shorten but shortening occurs in the third beat The R R interval remains about the same Strip b of Fig 2B shows the atrial rhythm remaining slightly unstable and irregular The P R intervals vary shortening and then lengthening markedly before the blocked beat so do the R R intervals vary lengthening and then shortening The maximally conducted P R interval is quite long 0.66 sec The blocked beat initiates a brief period of AVB in the middle portion of the lower strip with an unstable pathological axis elevated junctional rhythm (rate of 88 to 97) perhaps due to concealed antegrade discharge of the junctional pacemaker cell The acceleration may be due to phase 4 depolarization from the hypokalemia. Another possibility in the lower strip of Fig 2B is that all the P's are conducted except for P<sub>1</sub> P<sub>2</sub> conducting to the eighth QRS complex In strip c of Fig 2B the first group the P R intervals increase and then decrease with the first P R (0.1 sec) being slightly less than that just prior to the pause (0.23 sec) The R R is variable but the last R R is less than the first R R interval. The Wenckebach sequence ends in a blocked P (P<sub>1</sub>) pause followed by a JEB (R) with aberration perhaps due to a fascicular beat or to phase 4 depolarization the ensuing pause consists of a concealed conducted atrial impulse (P<sub>1</sub>) allowing conduction of the next sinus impulse introducing another Wenckebach period, the first P R of which is 0.18 sec The last P R is longer and the last R R narrower than those beginning the sequence The R P (R to blocked P) and R P (R to concealed conducted P) equals 0.45

and 0.64 sec, respectively The P R (conducted P to escape beat) interval is considerably greater 1.44 sec than the P<sub>1</sub> R (concealed P to the next conducted R) interval of 0.88 sec In strip d of Fig 2B the P R interval shortens prior to the pause and subsequent JEB with aberration Supernormal conduction (SNC) or a delay at two sites may explain this The R P is 0.40 sec The P R intervals preceding the JEB's in strips c and d are 0.23 sec The second QRS complex of strip e is probably an aberrant JEB while the last beat is conducted with a markedly prolonged P R interval (0.66 sec) In strip f of Fig 2B two Wenckebach periods are present The P R in the first ranges from 0.16 to 0.58 sec, suddenly prolonging before the blocked P the R R cycle narrows remains the same and then lengthens markedly before the block. The QRS of this prolonged conducted P wave the subsequent JEB (dissociated from P) and subsequently prolonged conducted QRS complex (P R of 0.56 sec)—the sixth to eighth QRS complexes—are aberrantly conducted. The seventh QRS complex is probably an accelerated JEB—actually the longer the P R interval, the closer the R of the conducted beat comes to the R of the escape beat—less likely it is conducted with a skipped P wave (the second P wave before the QRS complex being the conducted sinus impulse rather than the immediately preceding P) Again concealed conduction ensues in the tenth P and allows atrial conduction to manifest introducing the second sequence the last beat of which follows delayed AV conduction (0.64 sec) after the first three beats with essentially constant P R and R R intervals. Before the JEB the R P is 0.10 sec and the penultimate R P interval is 0.43 sec The R P intervals preceding the prolonged conducted beats (R P) are 0.43 0.60 and 0.46 sec respectively The P R intervals before the first and last prolonged conducted beats are 0.25 and 0.22 sec The R P before the conducted beats in strip c and strip f of Fig 2B are 0.64 and 0.15 sec, respectively

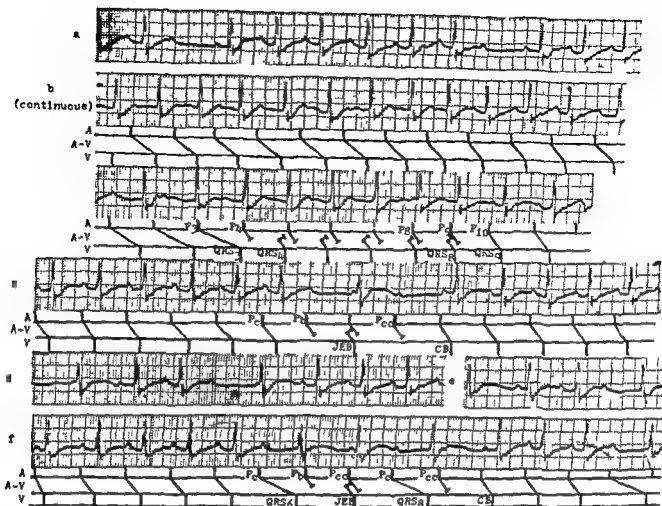


Fig 2B Lead II rhythm strips 6 AM  $\alpha$  to  $f$  See text  $\alpha$  AR = 85.90 Slight sinus arrhythmia P R intervals = 0.20 0.24 sec Atypical Wenckebach periods Concealed conduction  $b$  AR = 84.98 Sinus arrhythmia Atypical type 1 second degree AV block with markedly prolonged AV conduction followed by AV dissociation and an unstable accelerated junctional rhythm in the midportion of the lower strip Concealed conduction  $c$  AR = 85.88 Atypical type 1 second degree AV block A JEB with aberration follows the first Wenckebach sequence The second sequence results from a conducted atrial impulse aided by concealed conduction as the prior atrial impulse  $d$  supernormal conduction may explain the slight P R shortening before the pause  $e$  The second ventricular beat is aberrant and is probably a JEB while the last beat conducts at a prolonged P R interval of 0.66 sec  $f$  AR = 83.88 Atypical Wenckebach block JEB with aberration Concealed conduction allows AV conduction to culminate CB = conducted beat JEB = junctional escape beat  $P_a$  = blocked atrial impulse  $P_c$  = conducted atrial impulse  $P_{cc}$  = concealed atrial impulse

(the II P interval is anticipated to be longer than the R P, and thus partial penetration occurs) The P R distances are the same (P R longer R R of JEB shorter) the P subsequent R interval is greater than the P R interval so a conducted beat occurs The P R intervals are 1.24 and 0.88 sec The atrial impulses in pauses of Wenckebach sequences have been considered to be either conducted or blocked with JEBs. " However the brilliant analyses of Langendorf and Pick have offered methods for distinguishing escape beats following blocked atrial impulses from conducted beats permitted by concealed atrial impulses.

Fig 3 ECG taken six hours later (potassium of 4.0 mEq/L one-half hour prior) is compatible with typical hypokalemia showing slight ST segment sagging and prominent U waves the QRS width is normal

A tracing Fig 4 done 7½ hours later was normal

## Discussion

Cardiac arrhythmias such as multifocal ventricular ectopic beats and VT and/or conduction

disturbances have occurred during or between attacks of the various types (hyper normo and hypokalemic) of periodic paralysis.<sup>31, 33</sup>

**Conduction disturbances in periodic paralysis and hypokalemia** In 1941 Stoll and Nisnewitz<sup>28</sup> observed a patient with HPP who demonstrated P-R interval prolongation and dropped beats. Atropine normalized the P-R interval and raised the T wave suggesting increased vagal tone during the attacks.<sup>36</sup> Renal hypokalemia patients may show first and second degree AV block.<sup>37</sup> Other cases of HPP have shown hypertension, bradycardia, cardiomegaly, atrial fibrillation (Af), ST and T abnormalities, QT prolongation and marked first and both types of second-degree AV block during spontaneous (potassium of 1.1 mEq/L) and induced attacks.<sup>38</sup> The latter

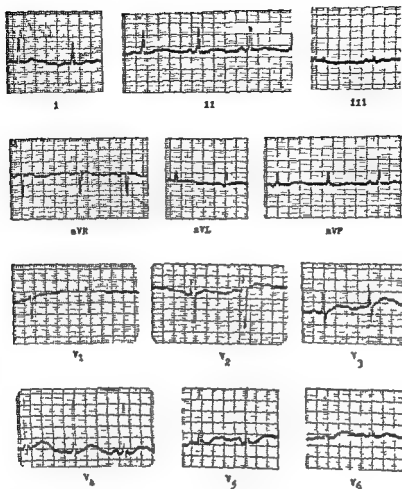


Fig 3 ECG 12 noon Rate = 62 PR = 0.16 sec QRS = 0.08 sec QT = 0.42 sec QU = 0.50-0.55 sec axis + 30 degrees Prominent U waves (1 mm height) but the T/U ratio = 1 or greater Slight ST segment sagging

investigators<sup>1,2</sup> suggested as causative a combined transient change in the conducting fibers from hypokalemia and augmented thyroxine. Another case demonstrated the usual electrocardiographic pattern but the serum potassium was never lower than 3.2 mEq/L.<sup>3</sup>

Stewart and colleagues<sup>4</sup> in 1940 were probably the first to record in the English language a case of familial periodic paralysis (FPP) and hypokalemia depicting QRS complex widening. A 19 year old male's ECG (with half normal serum potassium) showed during an attack of paralysis PR QRS (0.12 to 0.20 sec wide depending upon the placement of junction J and the QRS was of right bundle branch block type) and QT interval prolongation which corrected with potassium chloride (KCl) and subsidence of the attack. They cited one similar case from the German literature. Brown and associates<sup>5</sup> cited another case

of FPP (their Fig 3) in whom the ECG showed slight impairment of intraventricular conduction (QRS of 0.11 to 0.12 sec) which was attributed to coronary heart disease. Transient widening and splintering of QRS complexes have rarely been observed in hypokalemic diabetic acidosis. In Henderson's two patients the QRS width was up to 0.14 sec in the lateral precordial leads (normal width in other leads) in one female with Af and ranged from 0.16 to 0.20 sec in the chest leads (normal in bipolar leads) of the second female whose later tracing had narrower complexes with an even lower potassium level. Both of these patients died. A possible role of intracellular potassium was considered as there was no correlation between the serum potassium and the degree of cardiographic abnormality. Surawicz<sup>6</sup> reported one case with a slur at the foot of the descending limb of the R wave and a QRS width



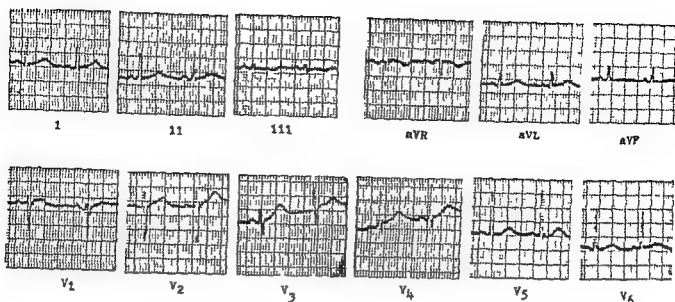


Fig 4 ECG 7:30 PM Rate = 80 PR = 0.13 sec QRS = 0.08 sec QT = 0.40 sec axis = +35 degrees Normal electrocardiogram

of about 0.12 sec. However, he believed these were rare in hypokalemia and seemed to appear only at very low potassium levels or in combination with other factors such as acidosis.<sup>11</sup> Sarma's two cases<sup>12</sup> of hypochloremic alkalosis and hypokalemia had mild to moderate increases in width (about 0.11 sec) and amplitude of the QRS complexes and in the PR length. Recent reviews<sup>13</sup> and textbooks of cardiology<sup>14</sup> recognize occasional AV conduction defects, but only slight diffuse QRS widening without change in configuration in advanced hypokalemia; the magnitude of these is relatively small and can be recognized only in serial tracings since the measured intervals remain within normal limits.<sup>1</sup>

Probably the most striking case ever published and that most resembling ours is the 6 year old boy with cystinosis, severe metabolic imbalance and hypokalemia (1.6 mEq/L) reported by Cherry and Surawicz.<sup>15</sup> This patient's ECG revealed uniform QRS widening (0.14 to 0.18 sec) associated with first and second degree Wenckebach AV block and multiple ectopic, fusion, and escape beats during intravenous administration of glucose in salt solution. After giving potassium chloride intravenously a short ST segment followed by a T wave merged to the U wave was interposed followed by disappearance of the AV block and narrowing of the QRS width to normal. Initial masking of the characteristic features of hypokalemia was attributed to the tachycardia and IVCD; the former fusing the T with the U and P waves while the secondary ST and T changes of the latter directed oppositely to the

wide terminal portion of the QRS counteracts the primary ST-T changes of hypokalemia. A long R-R interval separating the T from the P, and the potassium chloride infusion unmasked the true nature of the condition, in spite of its mimicry of a hyperkalemic pattern. The Lead V<sub>1</sub> QRS duration was only 0.10 sec and there was a short ST segment visible. These investigations and the studies of Surawicz<sup>14</sup> indicating that the short slurred segment following the QRS corresponds to the shortened initial phase of repolarization (phase 2), and previously published studies of severe hypokalemia with widening affecting mainly the terminal portion of the QRS making distinction between a terminal slur of the S wave or a short ST segment very difficult, were emphasized by the authors.<sup>16</sup> This dilemma was also recognized in our case. These investigators believed that even if the atypical short ST segment were not incorporated into the QRS the latter still showed generalized widening as it narrowed from 0.10 to 0.06 sec after administration of potassium.

In Conis' case<sup>17</sup> (potassium of 2.5 mEq/L) there was PR prolongation but no or very minimal QRS widening. Attacks of paralysis were induced but electrocardiographic changes did not correlate with the serum potassium levels even down to a potassium level of 1.48 mEq/L. In a 30 year old female without heart disease right bundle branch block was observed during induced hypokalemia. In the presence of orthograde blocking the impulses entered the right bundle branch in a retrograde manner; the velocity of

retrograde activation being dependent upon heart rate and seen as a spike after the ventricular potentials or His bundle recordings<sup>34</sup>

**Experimental studies—hypokalemia and conduction defects** In contrast to human clinical experience studies in experimental animals with hypokalemia reveal delay and block of AV transmission in pigs fed a low potassium diet and in the isolated frog turtle and rabbit heart when exposed to low potassium perfusions glucose and insulin infusions and low potassium dialysis can induce AV conduction disturbances in dogs Intraventricular conduction delay is less pronounced but has been described in the rabbit turtle and dog and in calves fed a potassium free diet<sup>6 10 17 25 37 38</sup>

Surawicz Gettes and associates<sup>39</sup> found that perfusing isolated rabbit hearts with low potassium solutions caused a prolonged phase 3 and shorter phase 2 and an increased amplitude duration and upstroke velocity of the action potential (AP) reflected in a progressively diffuse widening and augmented amplitude of the QRS complex without a change in shape This slowed intraventricular conduction velocity was attributed to hyperpolarization—a decreased resting membrane potential (RMP) Sinus or junctional bradycardias with increases in P R and R P intervals developed followed by more advanced AV conduction defects such as 2:1 Wenckebach and complete AV blocks These changes reverted to normal on infusing Krebs Henselet solution

Paes de Carvalho and Langan<sup>40</sup> observed impaired AV nodal transmission and block in the isolated intact Langendorff perfused rabbit heart when the potassium fell below 2 to 2.7 mM and variable AV block with irreversible damage to propagation at levels less than 1 mM There was a slight tendency to QRS prolongation and the H V interval lengthened minimally AV conduction usually corrected on raising serum potassium levels A decreased AP amplitude and rate of depolarization of AV nodal fibers depressing intranodal conduction and aggravating Type 1 block and enhancing diastolic depolarization of His Purkinje cells was found by Watanabe<sup>41</sup> Potassium administration may shorten the P R interval in hypokalemic patients however in others AV propagation may improve on lowering the serum potassium

**Pathophysiology** The mechanism for trans-

mission delay in hypokalemia has not been clarified but may involve one or more of the following (1) hyperpolarization (more negative RMP) of the myocardial cell in diastole requiring a stronger stimulus to bring the transmembrane potential to threshold potential (TP) (2) excitation of the cell before complete repolarization producing a slower upstroke of the AP leading to slowed rates of depolarization and wider QRS complexes (3) the greater sensitivity to vagal stimulation Reentry and automaticity from augmented phase 4 depolarization enhance arrhythmias<sup>6 10 17 25 35 38</sup>

Although controversial the ECG appears to reflect extracellular potassium and the myocardial cell membrane potassium gradient<sup>3 42</sup> This is supported by the observation that the intracellular concentration of potassium was not significantly different in hearts perfused with low normal and high concentrations of potassium<sup>4</sup> and the fact that in FPP the ECG may reflect rapidly changing plasma potassium levels the electrocardiographic changes occurring during an attack of paralysis are those characteristic of hypokalemia but more severe than those seen in normal persons at comparable levels of serum potassium Serum potassium falls but the status of muscle potassium is not settled<sup>43</sup> In our patient muscle potassium was very low Authorities agree that the actual level of serum potassium during an attack whether or not accompanied by an arrhythmia is unlikely to be crucial<sup>4</sup> Also these electrocardiographic changes are believed to be due to the electrophysiological alterations rather than to the anatomical lesions of hypokalemia<sup>4 5</sup>

The initial ECG (Fig 1) shows ST elevations in Leads I aV<sub>F</sub> aV<sub>L</sub> and V<sub>1-3</sub>, a rare finding in hypokalemia<sup>44</sup> This tracing resembles that of hyperkalemia more than that of severe hypokalemia an observation appreciated once before<sup>45</sup> and the AV block and ST segment depression have been said to be the same in these conditions except for low T waves in the latter

Originally Surawicz and colleagues<sup>46 47</sup> interpreted the QRS alteration as a slurred terminal portion of the depolarization process in each heart muscle element Later works view the ventricular complex in advanced hypokalemia as being diffusely widened from an IVCD due to generalized slowing of propagation in the ventricular myocardium and/or Purkinje fibers and not

from a focal block in a bundle branch.<sup>3, 4, 15, 27</sup>

So as reviewed studies are inconsistent some purporting that clinical hypokalemia never produces any significant consistent QRS complex widening,<sup>6, 15, 16</sup> others accepting slight widening (0.01 to 0.03 sec),<sup>3, 4, 11, 2, 47, 30, 31</sup> or more pronounced widening particularly in children,<sup>1, 4, 13, 1</sup> as well as AV conduction defects.

**Atrioventricular conduction defects.** More over the AV conduction abnormalities in our patient are most interesting. Atypical forms of Wenckebach block are present,<sup>16, 3</sup> and without His bundle recordings these can offer difficulty in recognizing the nonconducted atrial impulse. Various manifestations of concealed conduction (atrial echo beat, concealed AV nodal re entry, etc.) and supernormal (Type A) conduction may play a critical role, the delayed JEB provides sufficient time for atrial propagation, so that in a record with unquestionable AV nodal escapes contrary to the rule, the longer ventricular cycles terminate with conducted beats while shorter cycles terminate with JEB's. Langendorf and Pick<sup>11</sup> state that if the distance between the concealed atrial impulse (P<sub>c</sub>) (the blocked P following P) and the subsequent R (P-R) approaches the established conducted atrial impulse to escape distance (P-R) the R represents an escape beat if P-R is considerably shorter, then the beat terminating the pause engendered by the concealed P is a conducted beat.<sup>11, 1</sup>

Concealed and supernormal conduction have been induced experimentally in dogs from potassium induced depression of AV conduction.<sup>9</sup> Changing levels of serum potassium (2.7 mM/L to hyperkalemia) experimentally have little effect on the sinoatrial node<sup>10, 19</sup> but a vagal effect on the AV node producing Wenckebach block may become manifest under conditions of nonresponsiveness of the former to vagal stimulation.<sup>1</sup> Hypokalemia augments the cardiac sensitivity to vagal stimulation and this enhanced tone may induce marked sinus bradycardia and AV transmission defects,<sup>10, 11</sup> a mechanism perhaps of import in our patient.

Aberrancy of the JEBs and the slowly conducted beats (prolonged P-R intervals) manifesting late may be attributed to Mahaim fiber conduction fascicular origin from the left bundle branch phase 4 depolarization shift of the TP

toward zero, concealed escapes and hypopolarization.<sup>2, 7, 74</sup> The studies of Singer and colleagues<sup>7</sup> revealed that the development of phase 4 depolarization with a decrease in potassium conductance was facilitated by lowering the concentration of potassium in the Tyrode solution. They believed that such reduction in diastolic potential could lead in the intact heart to widespread involvement of the Purkinje system producing SNC, aberrancy of JEB's, AV block, bundle branch block, and intraventricular block of diffuse and nonspecific pattern.

Although ventricular arrhythmias with conspicuous QRS widening and second degree sinoatrial and AV nodal block have been observed previously,<sup>14, 17</sup> as far as we can determine our patient with periodic paralysis and severe hypokalemia demonstrates the most striking alterations of the QRST complexes and AV conduction that have been documented in these conditions.

## Summary

This article documents striking atrioventricular and intraventricular conduction disturbances in marked hypokalemia, in a Negro male with periodic paralysis. The authors discuss cardiac conduction in hypokalemia.

## REFERENCES

1. Pick A. Arrhythmias and potassium in man. *AM HEART J* 72:295 1966.
2. Davidson S and Surawicz B. Ectopic beats and atrioventricular conduction disturbances in patients with hypokalaemia. *Arch Intern Med* 120:280 1967.
3. Surawicz B. Relationship between electrocardiogram and electrolytes. *AM HEART J* 73:814 1967.
4. Surawicz B. Arrhythmias and electrolyte disturbances. *Bull N Y Acad Med* 43:1160 1967.
5. Lichten E, Chadda K and Feng S. Atrial pacing in the treatment of refractory ventricular tachycardia associated with hypokalemia. *Am J Cardiol* 30:550 1973.
6. Fisch C. Relation of electrolyte disturbances to cardiac arrhythmias. *Circulation* 47:408 1973.
7. Kleinfield M and Rozanski J. Self induced hypokalemia. *N Y State J Med* 75:2229 1970.
8. Zipes DP. Electrolyte derangements in the genesis of arrhythmias. In: *Cardiac arrhythmias*. Dreifuss L S and Lakoff W, eds. New York 1973. Grune & Stratton Inc. pp 55-69.
9. Brown M R, Currens J H and Marchand J F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *JAMA* 124:545 1944.
10. Ganggacomo J and Hlnt R. Atrioventricular conduction disturbances with hypokalemia in renal tubular acidosis. *J Electrocardiol* 7:273 1974.
11. Chung E K. Electrocardiographic findings in hypokalemia. *Postgrad Med* 51:287-287 1972.

12. Chung E K Principles of cardiac arrhythmias Baltimore 1971 The Williams & Wilkins Company pp 484 485
13. Fowler N O Cardiac diagnosis and treatment Hagers town, Md. 1976 Harper & Row Publishers p 1024
14. Davis M H and Fisch C Potassium and arrhythmias Geriatrics 25 108 19/0
15. Cherry J D and Surawicz H Unusual effects of potassium deficiency on the heart of a child with cystic nosis, Pediatrics 30 414 1969
16. Solinas L and LoSardo S Le flottement du PQ Arch. Mal. Coeur 48 871 1952
17. Chesler E and Schamroth L The Wenckebach phenomenon associated with aortic atherosclerosis Br Heart J 19 577 1957
18. Dressler W and Swiller S L Atypical Wenckebach periods with dropped atrial beats Am J Cardiol 2 575 1958
19. Myerburg R J Goodman J S and Marmott H J L Atypical forms of the Wenckebach phenomenon Am J Cardiol 11 418 1963
20. Schamroth L The disorders of cardiac rhythm Oxford and Edinburgh 1971 Blackwell Scientific Publications pp 296-297 469 471
21. Bilitch M A manual of cardiac arrhythmias Boston 1971 Little Brown & Company 1971 p 193
22. Cosby R W and Bilitch M Heart block New York 1977 McGraw Hill Book Company Inc 1972 pp 19-20
23. Abernathy W S A rare form of Wenckebach atrioventricular block J Electrocardiol. 7 183 1974
24. Denes P Levy L Pick A et al. The incidence of typical and atypical A V Wenckebach periodicity Am. Heart J 89 26 19/5
25. Friedman H S Gomes J A C and Huft J I An analysis of Wenckebach periodicity J Electrocardiol. 8 307 1973
26. Masuma R A Ertem G E, and Yers Z Aberrancy of junctional escape beats. Evidence for origin in the fascicles of the left bundle branch Am J Cardiol 29 351 1970
27. Singer D H Lazzara R and Hoffman B F Interrelationships between automaticity and conduction in Purkinje fibers Circ Res 21 537 1967
28. Pick A Langendorf R and Katz L N The supernormal phase of atrioventricular conduction Circulation 26 388 1967
29. Moe G K Childers R W and Mendeth J An appraisal of supernormal A V conduction Circulation 38 5 1968
30. Knoebel M H and Fisch C Accelerated junctional escape A clinical and electrocardiographic study Circulation 50 151 1974
31. Langendorf R and Pick A Concealed conduction Further evaluation of a fundamental aspect of propagation of the cardiac impulse Circulation 13 381 19/6
32. Childers R Concealed conduction Med Clin North Am 60 149 19 6
33. Lasak R P Lebeau J Tucker S H et al Hyperkalemic periodic paralysis and cardiac arrhythmias Neurology 22 810 1970
34. Klein R Ganelin R Marks J F et al Periodic paralysis with cardiac arrhythmia J Pediatr 62 371 1963
35. Levitt L P Rose L L and Dawson D M Hypokalemic periodic paralysis with arrhythmia, N Engl J Med 286 53 19 2
36. Stoll B and Nemenitz S Electrocardiographic studies in a case of periodic paralysis Arch Intern Med 67 755 1941
37. Earle D P Sherry S Eichna L W., et al. Low potassium syndrome due to defective renal tubular mechanisms for handling potassium Am J Med 11 283 1951
38. Perelson H H and Cosby R S The electrocardiogram in familial periodic paralysis, AM HEART J 37 1126 1949
39. Vastola E F and Bertrand C A Intracellular water and potassium in periodic paralysis, Neurology 6 523 1956
40. Copen A J., and Reynolds E H Electrolyte and water distribution in familial hypokalemic periodic paralysis J Neurol Neurosurg Psychiatry 29 107 1966
41. Corbett V A and Nuttall F Q Familial hypokalemic periodic paralysis in blacks Ann Intern Med 63 1975
42. Muenthongchun N Vejajiva A and Jambala B Disturbance of atrioventricular conduction in a patient with thyrotoxic periodic paralysis J Med. Assoc. Thailand 53 314 1970
43. Van Buchem F H P The electrocardiogram and potassium metabolism Electrocardiographic abnormalities in primary aldosteronism and familial periodic paralysis Am J Med 23 376 1957
44. Stewart H J Smith J J and Mulhorat A T Electrocardiographic and serum potassium changes in familial periodic paralysis, Am J Med Sci. 189 789 1940
45. Janota O and Weber K Abhandlungen aus der Neurologie Psychiatrie Psychologie und ihren Grenzgebieten Berlin 19/8 S Karger AG No 46
46. Henderson C B Potassium and the cardiographic changes in diabetic acidosis Br Heart J 15 87 1953
47. Surawicz B Lepeschkin E The electrocardiographic pattern of hypokalaemia with and without hypocalcaemia Circulation 8 801 1953
48. Sarma R N Unusually tall and narrow U waves simulating hyperkalemic T waves Report of 2 cases of hypochloremic alkalosis with hypokalemia AM HEART J 70 397 1965
49. Vander Ark C H Ballantyne F and Reynolds E W Electrolytes and the electrocardiogram Cardiovasc Clinics 6 99 1973
50. Wenger M., and Epstein F H Signs and symptoms of electrolyte disorders, Yale J Biol. Med 43 76 19/0
51. Wenger M K and Herndon E G Endocrine and metabolic disorders chapter 82, in The heart Hurst J W ed New York 1974 McGraw Hill Book Company Inc., p 1499
52. Wenger N K Myocardial involvement in systemic disease chapter 75 in The heart Hurst J W ed New York, 1974 McGraw Hill Book Company Inc p 1360
53. Batsakis J G Degenerative lesions of the heart chapter X in Pathology of the heart and blood vessels Gould S E ed. Springfield Ill, 1968 Charles C Thomas Publisher p 494
54. Surawicz B Lepeschkin E Herrlich H C., et al Effect of potassium and calcium deficiency on the monophasic action potential, electrocardiogram and contractility of isolated rabbit hearts Am J Physiol 188 1302 19 9
55. Cont, N K The myocardium in periodic paralysis Postgrad. Med J 45 691 1969
56. Neuss, H Nowak F G and Schlepper M Right bundle branch block with retrograde activation of the right bundle in hypokalaemia Analysis with deriva

from a focal block in a bundle branch.<sup>3, 4, 13, 17</sup>

So as reviewed studies are inconsistent, some purporting that clinical hypokalemia never produces any significant consistent QRS complex widening,<sup>11, 14</sup> others accepting slight widening (0.01 to 0.03 sec)<sup>3, 4, 11, 13, 17, 20, 21</sup> or more pronounced widening, particularly in children,<sup>1, 11, 13</sup> as well as AV conduction defects.

**Atrioventricular conduction defects.** More over the AV conduction abnormalities in our patient are most interesting. Atypical forms of Wenckebach block are present,<sup>16, 17</sup> and without His bundle recordings these can offer difficulty in recognizing the nonconducted atrial impulse. Various manifestations of concealed conduction (atrial echo beat, concealed AV nodal re entry, etc.) and supernormal (Type A) conduction may play a critical role, the delayed JEB provides sufficient time for atrial propagation, so that in a record with unquestionable AV nodal escapes, contrary to the rule the longer ventricular cycles terminate with conducted beats while shorter cycles terminate with JEBs. Langendorf and Pick<sup>18</sup> state that if the distance between the concealed atrial impulse (P') (the 'blocked P' following P) and the subsequent R (P-R) approaches the established conducted atrial impulse to escape distance (P-R'), the R represents an escape beat if P-R is considerably shorter than the beat terminating the pause engendered by the concealed P is a conducted beat.<sup>18, 19</sup>

Concealed and supernormal conduction have been induced experimentally in dogs from potassium induced depression of AV conduction.<sup>4</sup> Changing levels of serum potassium (2.7 mM/L to hyperkalemia) experimentally have little effect on the sinoatrial node,<sup>20</sup> but a vagal effect on the AV node producing Wenckebach block may become manifest under conditions of nonresponsiveness of the former to vagal stimulation.<sup>1</sup> Hypokalemia augments the cardiac sensitivity to vagal stimulation and this enhanced tone may induce marked sinus bradycardia and AV transmission defects,<sup>10, 11</sup> a mechanism perhaps of import in our patient.

Aberrancy of the JEBs and the slowly conducted beats (prolonged P-R intervals) manifesting late may be attributed to Mahaim fiber conduction, fascicular origin from the left bundle branch phase 4 depolarization shift of the TP

toward zero, concealed escapes and hypopolarization.<sup>1, 17, 21</sup> The studies of Singer and colleagues<sup>22</sup> revealed that the development of phase 4 depolarization with a decrease in potassium conductance was facilitated by lowering the concentration of potassium in the Tyrode solution. They believed that such reduction in diastolic potential could lead in the intact heart to widespread involvement of the Purkinje system producing SNC, aberrancy of JEBs, AV block bundle branch block, and intraventricular block of diffuse and nonspecific pattern.

Although ventricular arrhythmias with conspicuous QRS widening and second degree sinoatrial and AV nodal block have been observed previously,<sup>1, 17</sup> as far as we can determine our patient with periodic paralysis and severe hypokalemia demonstrates the most striking alterations of the QRST complexes and AV conduction that have been documented in these conditions.

### Summary

This article documents striking atrioventricular and intraventricular conduction disturbances in marked hypokalemia, in a Negro male with periodic paralysis. The authors discuss cardiac conduction in hypokalemia.

### REFERENCES

- Pick A. Arrhythmias and potassium in man. *Am Heart J* 72:295 1966.
- Davidson H and Surawicz H. Ectopic beats and atrioventricular conduction disturbances in patients with hypokalemia. *Arch Intern Med* 120:260 1961.
- Surawicz H. Relationship between electrocardiogram and electrolytes. *Am Heart J* 73:814 1967.
- Surawicz H. Arrhythmias and electrolyte disturbances. *Bull N Y Acad Med* 43:1160 1967.
- Lehstein F, Chadda K and Fenig S. Atrial pacing in the treatment of refractory ventricular tachycardia associated with hypokalemia. *Am J Cardiol* 30:550 1972.
- Fisch C. Relation of electrolyte disturbances to cardiac arrhythmias. *Circulation* 47:408 1973.
- Kleinfield M and Rozanski J. Self induced hypokalemia. *N Y State J Med* 75:2229 1975.
- Zipes D P. Electrolyte derangements in the genesis of arrhythmias. In: *Cardiac arrhythmias*. Dreifuss L S and Lakoff W, eds. New York 1973. Grune & Stratton Inc pp 55-69.
- Brown M H, Curtiss J H and Marchand J F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *JAMA* 124:545 1944.
- Gianguacomo J and Klim R. Atrioventricular conduction disturbances with hypokalemia in renal tubular acidosis. *J Electrocardiol* 7:273 1974.
- Chung L K. Electrocardiographic findings in hypokalemia. *Isotgrad Med* 51:285 287 1972.

# Isolated T wave alternans

Francisco Navarro Lopez MD FACC

Juan Cinca MD

Gnès Sanz MD

Alberto Penz MD

Jorge Magrina MD

Amadeo Betriu MD

Barcelona Spain

Isolated T wave alternans is characterized by changes in contour amplitude or polarity of the T or T U wave appearing with regular rhythmicity usually every other complex unaccompanied by any discernible modification of the QRS wave or gross changes in the cycle length

The phenomenon was described by Mines in 1913 and the first clinical example was apparently recognized by Padilla and Coasio in 1931. Occasional mention had been made of the transient postextrasystolic variety. After the advent of the precordial leads a complete electrocardiographic tracing was published by Kimura and associates<sup>1</sup> in 1963. Eleven cases have been described in the literature associated with acquired repolarization disturbances,<sup>2-7</sup> and 13 more were recently recognized by Schwartz and colleagues<sup>8</sup> who examined 28 reported cases of the Romano Ward syndrome. Its true incidence however as well as the clinical meaning and mechanisms involved still remain obscure.

Among other factors low serum calcium level may play a role in the production of the T wave alternans as suggested by Doherty and co-workers<sup>9</sup> and by Kimura and associates.<sup>1</sup> It is the purpose of this report to review briefly the literature and present two observations that give additional support to their hypothesis.

From the Clínica Unit Department of Medicine Hospital Clínico University of Barcelona Spain.

Received for publication Dec 30 1976

Accepted for publication Feb 19 1977

Reprint requests: Dr. Francisco Lopez MD Cardiac Unit Hospital Clínico Casanova, 143, Barcelona Spain.

## Case reports

**Case 1** A 16-year-old male patient entered the hospital presenting with acute glomerulonephritis hypertension and left heart failure. Physical examination disclosed a regular rhythm at 156 beats per minute a blood pressure of 160/115 mm Hg and a respiratory rate of 23. Weight was 28 kilograms. Pulmonary rales were present. The hematocrit was 37 per cent the hemoglobin 12 Gm and the urea nitrogen 64 mg per 100 ml. The sodium was 137 mEq the potassium 5 mEq the chloride 106 mEq and the carbon dioxide 17.6 mEq per liter. The pH was 7.38 and the pCO<sub>2</sub> was 26 mm Hg. The urine gave a positive test for protein and its density was 1010. Diuresis measured 690 ml the first 24 hours.

Treatment during the first two days included a total dosage of 0.6 mg. of intravenous Cedilanid Furosemide 10 mg intravenously and reserpine 0.5 mg intramuscularly were given every 6 hours. The heart rate lowered to 40 beats per minute the third day the blood pressure to 115/50 mm Hg and the respiratory rate to 23 per minute. Diuresis increased to 1,200 ml. The electrocardiogram and the vectorcardiogram recorded showed a 2:1 and occasionally a 3:1 T wave alternans and a few ventricular premature beats (Figs. 1 and 2). Striking changes of repolarization were very evident in the left precordial leads. T wave measured 0.75 mV negative and the corrected QT interval 0.75 sec in Lead V<sub>1</sub> changing alternately to 0.3 mV and 0.65 sec. Physical examination failed to disclose pulse alternans. The urea nitrogen was 30 mg the serum proteins 5.4 mg and the calcium 8.2 mg per 100 ml. The sodium was 158 mEq the potassium 3.6 mEq the chloride 108 mEq and the carbon dioxide 15 mEq per liter. The pH was 7.47 and the pCO<sub>2</sub> 32 mm Hg. To control the bradycardia 0.5 mg. of oxyprenolol bromide was administered intramuscularly and the T wave alternans ceased at a heart rate of 50 beats per minute.

**Case 2** A 60-year-old woman was admitted to the emergency room after two days of diarrhea abdominal cramps vomiting and fever. She had had a gastric operation two years before and followed irregular treatment for hypocalcemic tetany.

Physical examination showed poor general condition. Temperature was 39°C, pulse 93 beats per minute and blood

- tions from the bundle of His and the right bundle Z Kreislaufforsch 61 536, 1972
- 57 Surawicz D and Gettes L S Effect of electrolyte abnormalities on the heart and circulation chapter 21 in Cardiac and vascular diseases Conn H L and Horwitz O eds Philadelphia 1971 Lea & Febiger pp 541 42 545-49
  - 58 Gettes L S Surawicz B and Shine J C Effect of high K low K and quinidine on QRS duration and ventricular action potential Am J Physiol 203 1135 1962
  - 59 Paes de Carvalho A and Langan W B Influence of extracellular potassium levels on atrioventricular transmission Am J Physiol 205 375 1963
  - 60 Weller J M Lown B Hoigne N V et al Effects of acute removal of potassium from dogs Circulation 11 44 1955
  - 61 Tu W H Blair G O and Schlerf P R Removal of excess body potassium by hemodialysis Am J Physiol 199 671 1960
  - 62 Watanabe Y Effects of electrolytes and antiarrhythmic drugs on atrioventricular conduction chapter 26 in Symposium on cardiac arrhythmias Sandoe E Flemsted Jensen E and Olesen K H eds Sodertälje Sweden, 1970 A B Astra pp 545-547 551 552
  - 63 Musselman E E et al Complete atrioventricular block due to hypokalemia following ovariectomy Vet Med Small Anim Clin 71 155 1971
  - 64 Weaver W F and Burchell H B Serum potassium and the electrocardiogram in hypokalemia Circulation 21 505 1960
  - 65 Swales J D Hypokalemia and electrocardiogram Lancet 2 1364 1964
  - 66 Pearson C M and Kalanaraman K The periodic paralysis chapter 47 in The metabolic basis of inherited disease Stanbury J B Wyngaarden J and Fredrickson D S eds New York 1972 McGraw Hill Book Company Inc pp 1181 1183 84
  - 67 Rowland L P Lisak N P, Levitt L P, et al Periodic paralysis K level during arrhythmia N Engl J Med 287 50 1972
  - 68 Winsor T Electrolyte abnormalities and the electrocardiogram JAMA 203 347 1968
  - 69 Fisch C Feigenbaum H and Bowers J A Concealed conduction due to potassium Am J Cardiol 11 7 1963
  - 70 De Mello W C, and Hoffman B F Potassium ions and electrical activity of specialized cardiac fibers, Am J Physiol 199 1125 1960
  - 71 Gambetta M Denes P and Childers R W Vagally induced second degree A V block Mobitz Type 1 and the hyporeactive SA node Chest 62 159 1972
  - 72 Sarachek N S Bradycardia dependent bundle branch block Relation to supernormal conduction and phase 4 depolarization Am J Cardiol 25 737 1970
  - 73 Rosenbaum M H Eliazar M V Lazzari J O et al The mechanism of intermittent bundle branch block Relationship to prolonged recovery hypopolarization and spontaneous diastolic depolarization Chest 66, 1973
  - 74 El Shenf N Scherlag B J and Lazzari R Bradycardia dependent conduction disorders J Electrocardiol 9 1 1976
  - 75 Redleaf P D and Lerner I J Thiazide induced hypokalemia with associated major ventricular arrhythmias JAMA 206 1302 1968
  - 76 Curry P Stubbs W Fitchett D, et al Ventricular arrhythmias and hypokalaemia Lancet 2 231 1976 pp 964 1247
  - 77 Stubbs W A Bidirectional ventricular tachycardia in familial hypokalaemic periodic paralysis Proc R Soc Med 69 223 1976

# Isolated T wave alternans

Francisco Navarro Lopez MD FACC

Juan Cinca MD

Gines Sanz MD

Alberto Periz MD

Jorge Magnia MD

Amadeo Betriu MD

Barcelona Spain

Isolated T wave alternans is characterized by changes in contour amplitude or polarity of the T or T U wave appearing with regular rhythmicity usually every other complex unaccompanied by any discernible modification of the QRS wave or gross changes in the cycle length

The phenomenon was described by Mines<sup>1</sup> in 1913 and the first clinical example was apparently recognized by Padilla and Cossio in 1931 Occasional mention had been made of the transient postextrasystolic variety After the advent of the precordial leads a complete electrocardiographic tracing was published by Kimura and associates<sup>2</sup> in 1963 Eleven cases have been described in the literature associated with acquired repolarization disturbances and 13 more were recently recognized by Schwartz and colleagues<sup>3</sup> who examined 28 reported cases of the Romano Ward syndrome Its true incidence however as well as the clinical meaning and mechanisms involved still remain obscure

Among other factors low serum calcium level may play a role in the production of the T wave alternans as suggested by Doherty and co workers<sup>4</sup> and by Kimura and associates<sup>5</sup> It is the purpose of this report to review briefly the literature and present two observations that give additional support to their hypothesis

From the Cardiac Unit Department of Medicine Hospital Clinico (Barcelona) Spain

Received for publication Dec 30 1976

Accepted for publication Feb 7 1977

Reprint requests: F Navarro Lopez MD Cardiac Unit Hospital Clinico Case No. 143 B C.I.B. Spain

## Case reports

**Case 1** A 16-year old male patient entered the hospital presenting with acute glomerulonephritis hypertension and left heart failure Physical examination disclosed a regular rhythm at 156 beats per minute a blood pressure of 165/115 mm Hg and a respiratory rate of 73 V weight was 28 kilograms. Pulmonary rales were present The hematocrit was 37 per cent the hemoglobin 12 Gm and the urea nitrogen 6 mg per 100 ml The sodium was 137 mEq the potassium 64 mg the chloride 106 mEq and the carbon dioxide 17.6 mEq per liter The pH was 7.38 and the pCO<sub>2</sub> was 36 mm Hg The urine gave a positive test for protein and its density was 1010 Diuresis measured 690 ml the first 24 hours

Treatment during the first two days included a total dosage of 0.6 mg of intravenous Cedilanid Furosemide 10 mg intravenously and reserpine 0.5 mg intramuscularly were given every eight hours The heart rate lowered to 40 beats per minute the third day the blood pressure to 115/50 mm Hg and the respiratory rate to 23 per minute Diuresis increased to 1,200 ml The electrocardiogram and the vectocardiogram recorded showed a 1 and occasionally a 3 1 T wave alternans and a few ventricular premature beats (Figs 1 and 2) Striking changes of repolarization were very evident in the left precordial leads T wave measured 0.75 mV negative and the corrected QT interval 0.75 sec in Lead V changing alternately to 0.3 mV and 0.65 sec Physical examination failed to disclose pulse alternans The urea nitrogen was 3 mg the serum proteins 5.4 mg and the calcium 8.2 mg per 100 ml The sodium was 138 mEq the potassium 3.6 mEq the chloride 108 mEq and the carbon dioxide 25 mEq per liter The pH was 7.47 and the pCO<sub>2</sub> 37 mm Hg To control the bradycardia 0.5 mg of oxyprenonium bromide was administered intramuscularly and the T wave alternans ceased at a heart rate of 50 beats per minute

**Case 2** A 60-year old woman was admitted to the emergency room after two days of diarrhea abdominal cramps vomiting and fever She had had a gastric operation two years before and followed irregular treatment for hypocalcemic tetany

Physical examination showed poor general condition Temperature was 39 C pulse 93 beats per minute and blood



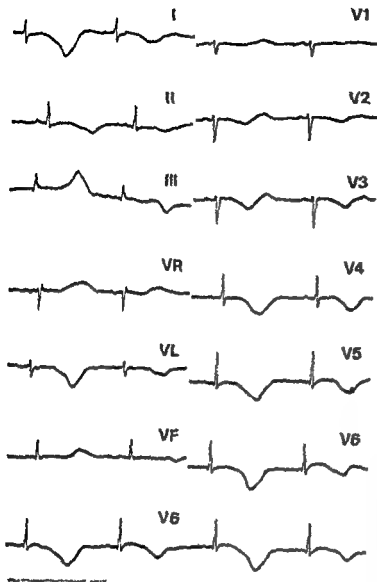


Fig 1 Electrocardiogram of Case I showing the T wave alternans. See text for discussion.

pressure 80/40 mm Hg. Chest x rays were normal. Laboratory findings included a hematocrit of 43 per cent and a white blood cell count of 13,000 per cubic millimeter. Blood urea nitrogen was 90 mg and glucose was 167 mg per 100 ml. Serum sodium was 137 mEq and potassium 2.2 mEq per liter. The electrocardiogram demonstrated T wave alternans.

Acute gastroenteritis was diagnosed and treated with antibiotics, fluid replacement, and infusion of 60 mEq of potassium. Twelve hours later the blood pressure was 100/50 mm Hg, the temperature 39.5°C, and signs of tetany were elicited. Laboratory data showed a hematocrit of 38 per cent, a urea nitrogen of 80 mg, glucose of 145 mg, serum proteins of 6.6 Gm, and calcium of 3 mg per 100 ml. Serum sodium was 139 mEq, potassium 3 mEq, and carbon dioxide 21 mEq per liter. The pH was 7.45 and the pCO<sub>2</sub> 30 mm Hg. Base excess was 5.6. The electrocardiogram was similar to the previous one and showed again T wave alternans (Fig 3). There was a sinus rhythm at a rate of 100 per minute and a left bundle branch block pattern. The QT interval measured 0.72 sec and 0.67 sec alternately. Carotid sinus stimulation on both sides was applied and followed by momentary interruption of the alternans (Fig 4) that was abolished with the infusion of 20

ml of a 10 per cent solution of calcium gluconate; the heart rate rising to 110 beats per minute and the blood pressure to 115/80 mm Hg. During the next hours recurrence of the alternans and frequent episodes of ventricular fibrillation ensued requiring electrical cardioversion on two occasions. Two hours later serum calcium level was 3.6 mg per 100 ml and the potassium was 2.4 mEq per liter. The ventricular instability was permanently abolished after additional infusions of 60 ml of the calcium solution were given in six hours, raising the calcium level to 5.8 mg per 100 ml, while the potassium concentration still was 2.5 mEq per liter. Oral treatment with calcium and potassium was followed by normalization of the electrolyte concentration and the ventricular repolarization in a week. The patient had a complete recovery.

## Discussion

**Electrocardiographic aspects.** The electrocardiograms of our two cases and the six collected from the literature with precordial leads<sup>7, 10, 12</sup> have the following features in common:

- 1 The left precordial leads show a giant negative T wave, its voltage ranging between 0.75 and 2.2 mV negative, with an average of 1.2 mV, that reduced the amplitude in the following beat by a decrement that ranged between 0.35 and 3.5 mV (mean, 1.16 mV). In three cases<sup>8</sup> it was large enough to change its polarity in one or more leads. The horizontal axis of the more aberrant of the T waves was located in the right anterior quadrant, except in the case reported by Wellens<sup>10</sup> and in our second case, with the left bundle branch block.

- 2 The corrected QT intervals were severely prolonged; the longest duration measuring between 0.62 and 1.09 sec (mean, 0.76 sec).

- 3 The QT interval shortened every other beat by an amount that varied in the different cases between 0.28 and 0.05 sec (mean 0.10 sec). Due to their constant association with the T wave alternans, the long QT and the QT alternans probably should be considered genuine components of the electrocardiographic picture. In fact, according to current views of the T wave electrogenesis,<sup>14</sup> the changes in depth could be explained by non homogeneous changes in duration of the recovery.

- 4 An increased tendency to ventricular instability manifested by ventricular premature beats and ventricular fibrillation<sup>8, 11, 12</sup> well documented in Case 2 further emphasizes the electrocardiographic similarity with the congenital long QT syndrome of the Romano-Ward type where the episodes of T wave alternans and ventricular

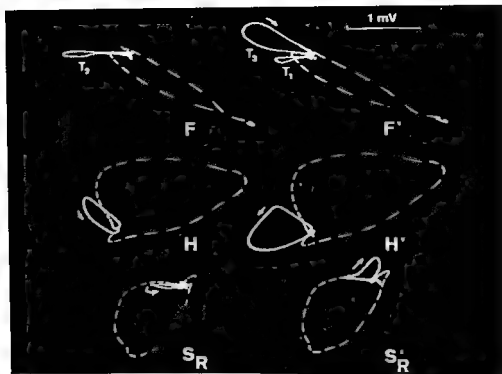


Fig 2 Vectocardiogram of Case 1 (Frank system) recorded at the same time as the electrocardiogram of Fig 1 F H S and F' H and S Frontal horizontal and right sagittal projections corresponding to the two different alternant T waves T<sub>1</sub> and T<sub>2</sub> two different T loops of the main 2:1 alternant sequence T<sub>1</sub> intermediate T loop of a 3:1 sequence See text for discussion



Fig 3 Electrocardiogram of Case 2 during T wave alternans See text for discussion

fibrillation are not uncommon'. The instability has been related to the severe prolongation of the QT interval and the temporal dispersion of the repolarization.

It has been suggested that the repolarization alternans may represent changes in the U rather than in the T wave<sup>2</sup> but this possibility

seems unlikely since the majority of the tracings show early as well as late repolarization changes<sup>11</sup>. The vectocardiogram showing also a better spatial display of the depolarization than the electrocardiogram seems to ratify that the T wave changes are independent of the ventricular activation (Fig 2). The concept of isolated

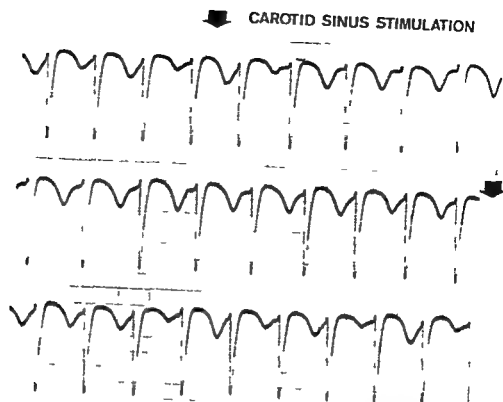


Fig 4 Case 2 Continuous tracing of Lead V<sub>1</sub> during carotid sinus stimulation showing the interruption of the T wave alternans Arrows point to the beginning and the end of the stimulation

Table 1 Published cases of T wave alternans

| Authors                           | Year | Age | Sex | Ca   | K   | Mg   | HR  | HD | HF | VF |
|-----------------------------------|------|-----|-----|------|-----|------|-----|----|----|----|
| 1 Padilla and Cossio <sup>1</sup> | 1931 | 60  | M   | -    | -   | -    | 54  | HF | -  | *  |
| 2 Lian et al                      | 1931 | 25  | M   | -    | -   | -    | 43  | HF | -  | -  |
| 3 Enselberg                       | 1952 | 50  | -   | -    | -   | -    | 107 | HD | -  | *  |
| 4 Hubbard et al                   | 1956 | 24  | F   | -    | -   | -    | 88  | HD | -  | -  |
| 5 Kimura et al                    | 1968 | 71  | F   | 7.8  | 3.6 | -    | 88  | HD | -  | -  |
| 6 Rickets et al                   | 1969 | 35  | M   | -    | 4.1 | 0.9  | 130 | HF | -  | -  |
| 7 Dolara and Pozzi                | 1971 | 57  | M   | 8.8  | 3.2 | -    | 125 | -  | -  | -  |
| 8 Fish                            | 1971 | 80  | M   | -    | -   | -    | 82  | HD | VF | -  |
| 9 Wellens                         | 1972 | 49  | F   | 10.2 | 4.8 | -    | 64  | HD | -  | -  |
| 10 Bashure et al                  | 1973 | 36  | F   | 7.5  | 1.3 | 77   | -   | VF | -  | -  |
| 11 Luomanmäki et al <sup>1</sup>  | 1975 | 63  | F   | 8.1  | 3.1 | 1.14 | 46  | HF | VF | -  |
| 12 Case 1                         | 1976 | 16  | M   | 8.2  | 3.6 | -    | 44  | HF | -  | -  |
| 13 Case 2                         | 1976 | 45  | F   | 3.2  | 2.8 | -    | 84  | -  | VF | -  |

Ca = Total serum calcium concentration in mg per 100 ml  
 HR = heart rate during T wave alternans HD = heart disease  
 HF = heart failure K = potassium concentration in mEq/liter  
 Mg = magnesium concentration in mg per 100 ml VF = episodes of ventricular fibrillation

= Electrocardiographic recording with precordial leads unavailable

alternans depends essentially on the inspection of the tracings<sup>9</sup> and theoretically even minor changes in depolarization could explain very apparent T wave alterations

**Clinical setting and etiology** Aside from the T wave alternans that appear in the congenital long QT syndrome and may be considered its congenital counterpart the acquired alternans has been observed in the following clinical situations (1) after rapid ACD blood transfusion during surgical hypothermia<sup>10</sup> (2) in patients with hypertensive heart disease and renal failure<sup>11</sup> associated with mild hypocalcemia<sup>12</sup> as in Case 1 (3) in severe pancreatic disease with shock renal failure, and low serum calcium and potassium<sup>13</sup>, (4) in severe chronic alcoholic ingestion with heart failure due to cardiomyopathy<sup>14</sup> or tetany<sup>15</sup> where T alternans was associated with hypomagnesemia and corrected by magnesium infusion and (5) after persistent supraventricular tachycardia in a patient with heart failure treated with quinidine and cardioversion<sup>16</sup>. Our Case 2 describes a new clinical condition with severe hypocalcemia due to parathyroid deficiency.

The possibility that calcium may have some bearing in the etiology of the T wave alternans is based mainly on its clinical observation after

ACD blood transfusion<sup>6, 13</sup> and during experimental hypocalcemia<sup>11, 15, 16</sup>. This view appears to be supported by the finding of mild hypocalcemia and a clinical setting compatible with calcium imbalance in the majority of the cases reviewed<sup>1, 2, 11, 12</sup> (Table I) although the pertinent information about the ionized serum calcium level is lacking. The severe hypocalcemia documented in Case 1 and the correction of the alternans after calcium infusion give additional evidence in favor of the causative role of the low calcium concentration.

Hypomagnesemia has also been implicated (Table I) and since ionized serum calcium and magnesium concentrations are closely related, it may be that their effects are mediated by a common mechanism. In addition, severe heart disease was a very common finding (Table I) absent only in Case 2 and in two previous observations.

The alternans was induced or intensified by deep inspiration, changes from recumbent to upright position, or by a sudden increase in the heart rate, and it was transiently suppressed in our case by carotid sinus stimulation, suggesting its interval dependence and/or the participation of an autonomic nervous system mechanism in eliciting alternans, as pointed out by Schwartz and colleagues<sup>2</sup>. On the contrary, the alternans was present in some cases (Table I) at low heart rates as in Case 1, where it was shown to disappear when the rate increased by the action of a vagolytic agent. In view of the clinical findings, it does not seem unreasonable to suspect that other factors known to prolong the QT, such as hypothermia, bradycardia, or quinidine, may have some facilitating effect.

Mechanism. The QT changes underlined are consistent with the hypothesis that the T wave alternans may be the electrocardiographic manifestation of the transmembrane action potential alternans. The alternation limited to rate and duration of the repolarization affecting mainly the phase 3 is easily induced in the isolated muscle strip preparations<sup>1, 11</sup> and shown to be influenced among other factors by the stimulation rate and the calcium concentration of the perfusion bath. It has been interpreted as due to an alteration of the calcium transport mechanisms of the cell membranes<sup>1</sup>.

Despite the apparently constant association of electrical and mechanical alternans in experi-

mental studies<sup>11, 18, 19</sup>, alternation of the systemic pressure has not been observed in man<sup>2, 11, 12</sup>.

## Summary

Two patients with isolated T wave alternans are reported with their vectocardiograms, their response to carotid sinus stimulation, and the response to calcium infusion in one of them with documented severe hypocalcemia. Eleven cases of the literature are briefly reviewed.

The alternans of the T wave appears with severe QT prolongation, QT alternans, and an increased tendency to ventricular fibrillation. The findings are consistent with the hypothesis that T wave alternans may be the electrocardiographic manifestation of the transmembrane action potential alternans and could be related in some cases to hypocalcemia.

## REFERENCES

1. Mines G R. On functional analysis by the action of electrolytes. *J Physiol* 45:188, 1913.
2. Padilla T and Cosmo P. Alterancia eléctrica ventricular. *La Semana Médica* 24:1573, 1931.
3. Kumura E and Yoshida K. A case showing electrical alternans of the T wave without change in the QRS complex. *AM HEART J* 64:391, 1963.
4. Lian C, Gilbert J, and Odinet J. Le pouls alternant dans ses rapports avec l'alternance électrocardiographique et le balancement ventriculaire électrique. *Arch Mal Coeur* 25:137, 1931.
5. Enseberg C D. The dying human heart. *Arch Intern Med* 90:15, 1959.
6. Hubbard T F, Neis D D, and Barmore J L. Severe citrate intoxication during cardiovascular surgery. *J A M A* 162:1534, 1956.
7. Rickets H N, Denson E K, and Haywood L J. Unusual T wave abnormality: Repolarization alternans associated with hypomagnesemia, acute alcoholism, and cardiomyopathy. *207:365*, 1969.
8. Dolara A and Pozzi L. Electrical alternation of T wave without change in QRS complex. *Br Heart J* 33:161, 1971.
9. Fish C. T wave alternans: an association with abrupt rate change. *AM HEART J* 81:817, 1971.
10. Wellens H J J. Isolated alternans of the T wave. *Chest* 64:319, 1972.
11. Bashore T, Rios J C, and Gorman P A. U wave alternans and increased ventricular irritability. *Chest* 64:377, 1973.
12. Luomanmaki A, Keikkilä J, and Hartikainen M. T wave alternans associated with heart failure and hypomagnesemia in alcoholic cardiomyopathy. *Eur J Cardiol* 3:167, 1975.
13. Doberty J E, and Hara M. The effect of citrate infusion on the electrocardiogram of the hypothermic and normothermic dog. *AM HEART J* 61:225, 1961.
14. Surawicz B. The pathogenesis and clinical significance of primary T wave abnormalities. In: *Advances in electrocardiography*. Schlant R C and Hurst J W, eds. New York, 1972, Grune & Stratton, Inc.

- 15 Kleinfeld M Gross M Electrocardiographic manifestations of hypocalcemia produced with ethylenediamine tetracetic acid *Am J Physiol* 187:479 1956
- 16 Navarro López F Cinca J Sanz G Magrín J and Betriu A Isolated T wave alternans induced by hypocalcemia in the dog (Abstr.) Abstract Book I Seventh European Congress of Cardiology Amsterdam Netherlands 1976 p 149
- 17 Maxwell M H and Kleeman C R Clinical disorders of fluid and electrolyte metabolism New York 1972 McGraw Hill Book Company Inc p 460
- 18 Kleinfeld M and Stein E Electrical alternans of components of action potential *Am Heart J* 75:54, 1968
- 19 Lu H Lange G and Brooks C H Comparative studies of electrical and mechanical alternation in heart cells *J Electrocardiol* 1:7 1968
- 20 Schwartz P J and Malliani A Electrical alternation of the T wave Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome *Am Heart J* 89:45 1975

#### Information for Authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

## Clinical, biochemical and pathological features of low renin ( primary ) hyperaldosteronism

J H Ferriss  
D G Beevers  
J J Brown  
D L Davies  
R Fraser  
A F Lever  
P Mason

A M Neville

J I S Robertson

Glasgow, Scotland and London, England

Some twenty years ago Conn<sup>1</sup> described a patient with hypertension, neuromuscular symptoms and renal potassium wasting. This was associated with increased urinary excretion of a sodium retaining hormone, subsequently shown to be aldosterone.<sup>2</sup> Removal of an adrenocortical adenoma resulted in a fall in blood pressure, correction of the biochemical abnormalities and disappearance of symptoms.<sup>3</sup> Further case reports rapidly appeared and with increasing experience less florid cases were recognized including asymptomatic patients and some in whom serum potassium was persistently normal.<sup>4-7</sup> The disorder has been called primary hyperaldosteronism.

Diagnosis was placed on a firmer footing by the observation that plasma renin concentration<sup>8</sup> and plasma renin activity<sup>9-11</sup> is suppressed in such patients. This distinguishes them from patients with hyperaldosteronism associated with malignant phase<sup>12</sup> or renovascular hypertension—so called secondary hyperaldosteronism<sup>13</sup>—in whom plasma renin concentration<sup>14,15</sup> and plasma renin activity<sup>16-18</sup> is increased. Thus the hallmarks of an aldosterone producing adenoma are hypertension, aldosterone excess

and low plasma renin commonly but not invariably with hypokalemia.<sup>19</sup>

Abnormalities qualitatively similar to these have also been reported in the absence of an adrenocortical tumor. The adrenal glands then show either hyperplasia of the zona glomerulosa often with nodular changes or a normal appearance.<sup>20-22</sup> The term primary hyperaldosteronism seems unsatisfactory for such patients without adrenal tumors since the adrenal changes may well be due to stimulation by an extra adrenal mechanism.<sup>23-25</sup> The terms idiopathic aldosteronism<sup>26</sup> and pseudo primary aldosteronism<sup>27</sup> have been applied to this group.

A few patients have been described with hypertension, aldosterone excess and low plasma renin in whom all the abnormalities were suppressed by dexamethasone.<sup>21</sup> Adrenal exploration in two such patients revealed adrenocortical hyperplasia. Occasional cases of hyperaldosteronism associated with adrenal carcinoma have also been reported<sup>28,29</sup> and rarely the syndrome has been associated with ovarian neoplasms.<sup>30</sup>

In view of the variability of the disorder it may be preferable to use low renin hyperaldosteronism as a generic term for patients in any of the above groups with or without an adrenocortical tumor. However the description primary hyperaldosteronism is often applied to all such patients and although not strictly correct we will

From the Medical Research Council, Blood Pressure Unit, and the University Department of Medicine, Western Infirmary, Glasgow, Scotland, and The Chester Beatty Research Institute, Royal Marsden Hospital, London.

Received for publication May 21, 1978.

Reprints request: Dr J I S Robertson, MRC Blood Pressure Unit, Western Infirmary, Glasgow G11 6TY, Scotland.

- 15 Kleinfeld M Gross M Electrocardiographic manifestations of hypocalcemia produced with ethylenediamine tetracetic acid *Am J Physiol* 187:479 1956
- 16 Navarro López F Cimca J Sanz G Magaña J and Betruu A Isolated T wave alternans induced by hypocalcemia in the dog (Abstr) Abstract Book I Seventh European Congress of Cardiology Amsterdam Netherlands 1976 p 149
- 17 Maxwell M H and Kleeman C R Clinical disorders of fluid and electrolyte metabolism New York 1972 McGraw Hill Book Company Inc p 460
- 18 Kleinfeld M and Stein E Electrical alternans of components of action potential *Am Heart J* 75:4 1968
- 19 Liu H Lange G and Brooks C H Comparative studies of electrical and mechanical alternation in heart cells *J Electrocardiol* 1:7 1968
- 20 Schwartz P J and Mathani A Electrical alternation of the T wave Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome *Am Heart J* 88:40-50

#### Information for Authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

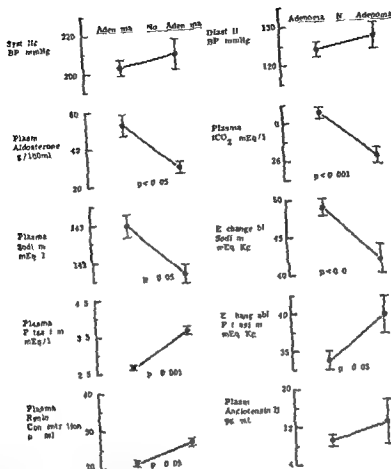


Fig 1 Comparison of variables in adenoma ( $N = 6$ ) and non adenoma ( $N = 17$ ) groups. Values are means  $\pm$  SEM.  $N = 3$  and 9 patients respectively.  $N = 29$  and 8 patients respectively.  $N = 14$  and 4 patients respectively.

statistical calculations were made on a Hewlett Packard 9910A calculator

### Clinical features

**Age and sex** Ages of the 136 patients ranged from 18 to 70 years (mean 46.5 years). There were 87 females (64 per cent) and 49 males (36 per cent). Of the 62 patients with a surgically proved adrenocortical adenoma 46 were female (74 per cent) while 9 of 17 proved non tumor patients were female (53 per cent).

Among those with histologically confirmed disease patients with an adrenocortical adenoma were significantly younger than those in whom no tumor was found (mean ages 42.1 and 50.7 years respectively  $p < 0.01$ ). When the sexes were analyzed separately this age difference persisted.

**Symptoms** A formal questionnaire on symptoms was not used and many patients were

initially investigated elsewhere. For these reasons a precise incidence of symptoms cannot be quoted. However a review of case records revealed that of the characteristic symptoms<sup>1,2</sup> headache (sometimes migranous) and nocturia were common. Other symptoms included muscle weakness and paresthesia (diuretic induced in at least five cases), thirst, polyuria and tetany. Sometimes none of the above symptoms were encountered; patients then presenting either with an incidental complaint or for routine examination.

**Blood pressure** Mean outpatient blood pressure while untreated ranged from 150/100 to 250/160 mm Hg (mean for series  $205/123 \pm 28/13$  SD). There was no significant difference in mean blood pressure between the surgically proved tumor and non tumor groups (Fig 1).

**Malignant phase hypertension** Renal biopsy was undertaken in 41 cases. Evidence of malig-



**Table 1** Classification of low renin ( 'primary') hyperaldosteronism

- 1 Aldosterone producing adrenocortical adenoma (Conn's syndrome)
- 2 Hyperplasia of the zona glomerulosa with micronodules (including a sub group with normal adrenal appearances)
- Rarely
- 3 Glucocorticoid—remediable hyperaldosteronism
- 4 Adrenocortical carcinoma
- 5 Hyperaldosteronism associated with ovarian tumors

also use this term. A classification of low renin hyperaldosteronism is shown in Table 1.

This paper reviews the clinical, biochemical, and pathological features of 136 patients with low renin ( 'primary') hyperaldosteronism, studied over a 12 year period. The published experience of other workers is also reviewed. Low renin hyperaldosteronism is defined here as hypertension associated with an elevated aldosterone value on at least one occasion and with a concurrent plasma renin concentration below the mean of the normal range. The condition must be clearly differentiated from low renin essential hypertension, where aldosterone is normal.<sup>40</sup> Details of some patients have been reported elsewhere.<sup>17, 28, 47, 53</sup> The differential diagnosis<sup>41</sup> and treatment<sup>42</sup> of this condition are discussed in separate papers.

#### Patients and methods

**Clinical data** All patients had a mean outpatient untreated diastolic blood pressure of 100 mm Hg or more, an elevated aldosterone value (plasma aldosterone > 18 ng/100 ml) or a raised aldosterone secretion rate) on at least one occasion and with a concurrent plasma renin concentration below the mean of the normal range (< 44 microunits per ml of International Standard Renin<sup>33</sup>). Eighty five patients were studied while taking a diet of fixed known normal intake of sodium and potassium (Na fixed for individuals at a particular point between 101 and 143 mEq/day. K similarly fixed at a point between 40 and 83 mEq/day). The remainder took a normal ward diet. No patient had taken diuretics, including spironolactone, potassium supplements or a restricted sodium diet for at least four weeks prior to investigation. Plasma cortisol concentration and/or urinary 17 oxogen steroids and 17 oxosteroids were normal in all cases.

Although plasma is preferable to serum for potassium measurement<sup>34</sup> plasma values were not always available and for this analysis plasma and serum estimations have both been used. Forearm exercise was avoided during venepuncture, as this may falsely raise potassium values.<sup>34</sup> Blood for measurement of plasma concentrations of renin, renin substrate, angiotensin II, and aldosterone was taken between 9.00 and 10.00 hours from an arm vein, patients having remained in bed and without food since 22.00 hours on the previous evening.

Since lower arterial pressures may be obtained in some patients when in the ward as compared with the outpatient clinic,<sup>35</sup> blood pressure readings used in this analysis were those taken in the outpatient department using a standard sphygmomanometer, with the patient seated. Except for the readings reported during treatment with spironolactone, amiloride or dexamethasone, all values were obtained in the absence of hypotensive drug therapy.

#### Laboratory techniques

Plasma electrolytes were measured by the Eppendorf flame photometer and serum electrolytes and blood urea by Auto Analyzer. Plasma renin concentration was measured by the method of Brown and associates,<sup>36</sup> (normal range 21 to 105 microunits per ml of International Standard Renin). Plasma renin substrate was measured by the method of Tree<sup>37</sup> (normal range 0.45 to 1.35  $\mu$ mol/l). Plasma angiotensin II concentration was measured by radioimmunoassay<sup>38</sup> (normal range 5 to 35 pg/ml). Plasma aldosterone concentration was measured by the double isotope derivative technique of Fraser and James<sup>39</sup> with minor modifications or by radioimmunoassay<sup>40</sup> (normal range up to 18 ng/100 ml). Gas liquid chromatography with electron capture detection<sup>41</sup> was used to measure plasma corticosterone (normal range 0.08–0.8  $\mu$ g/100 ml), plasma 11-deoxycorticosterone (normal 2–8  $\mu$ g/100 ml) and plasma 18-hydroxy-11-deoxycorticosterone (normal 20 to 160 ng/100 ml). Isotope dilution was used to measure total exchangeable sodium<sup>42</sup>, total exchangeable potassium<sup>43</sup>, "extracellular fluid volume"<sup>44</sup>, total body water<sup>45</sup> and plasma volume<sup>46</sup> using the respective isotopes <sup>22</sup>Na, <sup>40</sup>K, <sup>86</sup>Br, <sup>3</sup>H and <sup>125</sup>I.

The statistical technique of quadrat analysis has been reported elsewhere.<sup>47, 48</sup> This and other

before treatment in 32 patients in the adenoma group and in nine in whom a tumor was not found. Mean values were significantly higher in the former group (Fig 1).

**Plasma potassium and total exchangeable potassium.** Mean plasma potassium concentration before treatment ranged from 18 to 46 mEq/L and was significantly lower among patients in whom an adenoma was identified, compared with those in whom a tumor was not found (Fig 1).

Plasma potassium was measured on three or more occasions in each of 121 patients. Among these hypokalemia (plasma potassium  $< 3.7$  mEq/L) was persistent in 62 (51 per cent) and intermittent in 46 (38 per cent) while in 13 (11 per cent) plasma potassium was persistently normal. Hypokalemia occurred in all 62 patients with a proved adenoma and was persistent in 53. Among the 17 patients in whom a tumor was not found hypokalemia was persistent in four and intermittent in 10 but plasma potassium was persistently normal in three.

Total exchangeable potassium was measured before treatment in 29 and eight patients respectively in the groups with and without an adrenal cortical tumor. Mean values were significantly lower in the former (Fig 1).

**Plasma  $tCO_2$ .** Mean plasma  $tCO_2$  ranged from 22.0 to 37.0 mEq/L before treatment and was significantly higher among patients with a proved adenoma (Fig 1).

**Blood urea.** Mean blood urea before treatment ranged from 18.3 to 87.5 mg per cent being raised (greater than 40 mg per cent) in 27 cases. There was no significant difference in mean values between patients with a proved adenoma and those in whom an adenoma was not found. There was a significant inverse correlation between preoperative blood urea concentration and the fall in both systolic and diastolic pressure after surgery. There was also a significant inverse correlation between pretreatment blood urea and the fall in systolic pressure during treatment with spironolactone.

**Plasma renin concentration.** Mean individual plasma renin concentration before treatment varied from 3.2 to 56.8 microunits per ml. International Renin Standard (normal 2.1 to 10.0 microunits/ml) while plasma renin was below the mean of the normal range ( $< 4.4$  microunits/

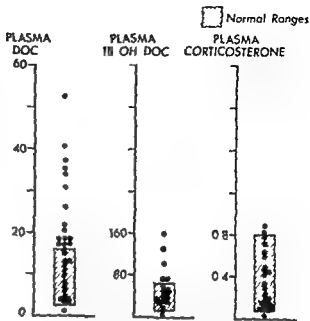


Fig 2 Plasma levels of DOC (ng/100 ml), 18-OH DOC (ng/100 ml) and corticosterone ( $\mu$ g/100 ml) in primary hyperaldosteronism.

ml) at least once in all. Values were significantly lower in the group with a proved adenoma compared with those in whom a tumor was not found (Fig 1).

**Plasma renin substrate.** Plasma renin substrate was measured before treatment in 16 patients; mean values ranged from 0.54 to 1.30  $\mu$ mol/L (normal 0.45 to 1.35  $\mu$ mol/L). There was no significant difference between patients with a proved adenoma and those in whom a tumor was not found.

**Plasma angiotensin II.** Plasma angiotensin II concentration was measured before treatment in 33 patients; mean values varied from 4.2 to 26.0 pg/ml (normal 5 to 35 pg/ml). Although mean values were lower in patients with a surgically proven adenoma compared with those in whom a tumor was not found, this difference did not reach conventional levels of statistical significance (Fig 1).

**Plasma 11 deoxycorticosterone (DOC).** Plasma DOC was measured in 26 patients (32 estimations). Values ranged from 1.1 to 52.5 ng/100 ml (normal 2.8 to 16 ng/100 ml) (Fig 2). Raised values were found in 13, including six of 12 patients with a proved adenoma and two of four patients in whom a tumor was not found at operation.

**Table II** Incidence of abnormalities in plasma aldosterone potassium, and renin concentrations in 54 patients with primary hyperaldosteronism in whom plasma aldosterone was measured on two or more occasions

|              | Elevated plasma aldosterone | Sub normal plasma K | Sub normal plasma renin |
|--------------|-----------------------------|---------------------|-------------------------|
| Persistent   | 22                          | 24                  | 1                       |
| Intermittent | 32                          | 24                  | 38                      |
| Not found    | 0                           | 6                   | 15                      |

nant phase hypertension (fibrinoid necrosis of the renal arterioles) was found in four. In two of these patients percutaneous biopsy was taken before starting treatment, while in the remaining two cases biopsy was taken at the time of operation. These findings may be an underestimate of the true incidence of fibrinoid necrosis before treatment. Renal biopsy is now undertaken in all cases coming to operation, but in recent years blood pressure has usually been well controlled with spironolactone, often for several months, affording time for severe renal lesions to heal. In one patient renal biopsy before treatment showed fibrinoid necrosis; subsequently blood pressure was well controlled with spironolactone and repeat biopsy several months later showed moderate hypertensive vascular changes only and fibrinoid necrosis was not observed.

Among the four patients with histological evidence of malignant phase hypertension papilledema was observed in one associated with bilateral hemorrhages and exudates. Hemorrhages and exudates without papilledema were seen in another but in the remaining two patients none of these abnormalities was observed.

**Vascular complications of hypertension.** Vascular complications of hypertension, such as stroke, myocardial infarction and angina occurred in 31 patients (22.8 per cent). In 23 cases such complications had occurred before the time of diagnosis and treatment. Details of these patients and their individual lesions are given elsewhere.<sup>11</sup>

The mean age of patients with vascular lesions was significantly greater than the mean age of those who did not suffer such complications. However, there was no significant difference in

the mean diastolic blood pressure between the two groups.<sup>11</sup>

**Renal and renovascular disease.** Eleven patients (8.4 per cent) had parenchymatous renal disease. Four had pyelographic evidence of chronic pyelonephritis (caliceal clubbing with thinning of the overlying renal cortex). Two patients had unilateral hydronephrosis, one associated with renal stone while a stone without evidence of obstruction was found in another. There was one case each of medullary sponge kidney, bilateral polycystic kidneys and renal carcinoma (confirmed at surgery). Another patient had hypertension and persistent proteinuria following a septic abortion complicated by acute renal failure seven years previously.

Six patients had bacteriological evidence of urinary tract infection but normal pyelograms.

Ten patients (7.4 per cent) had pyelographic evidence of renal artery stenosis. This was confirmed by arteriography, operation or autopsy in all except one. In the latter case arteriography was unsuccessful but pyelography and an isotope renogram also suggested the diagnosis. In no patient was there evidence to suggest whether the renovascular or adrenal lesion was first to develop.

Further details of the renal and renovascular lesions appear elsewhere.<sup>11</sup>

#### Biochemical abnormalities

**Plasma aldosterone.** Mean plasma aldosterone concentration before treatment ranged from 10.4 to 192.5 ng/100 ml although plasma aldosterone was above normal at least once in all cases. Plasma aldosterone was measured on two or more occasions in 54 patients, levels were persistently raised in 22 but only intermittently raised in 32 (see Table II).

Values were significantly higher among those patients in whom an adrenocortical adenoma was found at operation compared with those in whom a tumor was not identified (Fig. 1).

**Plasma sodium and total exchangeable sodium.** Mean plasma sodium concentration before treatment ranged from 135.7 to 150.5 mEq/L. Mean values were significantly higher in the group of patients with a proved adenoma compared with those in whom a tumor was not found (Fig. 1).

Total exchangeable sodium was measured

each patient was further subdivided according to the presence or absence of nodules in the attached and/or contralateral gland (Table III)

**Adrenal glands without tumor** The lesions in this group were subdivided into a number of patterns, according to the presence or absence of adrenal nodules and hyperplasia of the zona glomerulosa. The weight of surgically removed glands was recorded in 19 cases: twelve weighed less than 6 Gm and six were less than 4 Gm (upper limit of normal 6 Gm). In one patient parts of the adrenal cortex were normal histologically while others showed areas of hyperplasia of the zona glomerulosa with micronodules. This variation may account for the apparently normal appearance of the zona glomerulosa in one patient (Table III) as only biopsies of these glands were taken at surgery.

**Uncertain pathology** In this series we encountered three examples of single unilateral lesions 0.25 to 0.5 cm diameter which defied light microscopic classification as adenoma or macronodule. Each consisted of clear zona fasciculata type cells only with hyperchromatic nuclei and minimal or absent nuclear and cellular pleomorphism. These lesions had features of either a tumor composed of uniform large hybrid cells or of a macronodule with zona fasciculata type cells (see Discussion).

## Discussion

**Age and sex** This series again confirms that aldosterone producing adenomas are commoner among females.<sup>2,3</sup> However, no clear sex difference was apparent among the smaller group in whom a tumor was not found. In our experience patients with an adrenocortical adenoma are generally younger than those without an identifiable tumor, although others have not found this. There was no significant difference between the groups in mean blood pressure before treatment.

**Vascular complications** It has been suggested that patients with essential hypertension and low plasma renin have fewer vascular complications than those with normal or high renin levels, although this view has been widely challenged. Some believe that primary hyperaldosteronism is a comparatively mild form of hypertension and it has been suggested<sup>10</sup> that this may be related to low circulating renin levels.

In this series the high incidence of vascular

complications is in striking contrast to the good prognosis in low renin essential hypertension reported by Brunner and colleagues.<sup>7</sup> In addition there was histological evidence of malignant phase hypertension in four patients and other such cases have been described.<sup>11</sup> We find no evidence to support the view that primary hyperaldosteronism is a benign form of hypertension.

**Renal and renovascular lesions** A few reports suggest that chronic secondary hyperaldosteronism may sometimes lead to the development of autonomous aldosterone excess which persists when the original stimulus has been removed.<sup>4</sup> Secondary hyperaldosteronism may persist in salt losing nephritis when the sodium depletion has been corrected.<sup>12</sup> Secondary hyperaldosteronism associated with malignant phase hypertension may occasionally persist when the blood pressure has been controlled and plasma renin levels return to normal.<sup>4</sup> Autonomy in response to prolonged stimulation has been reported in other endocrine disorders. Long standing hypocalcemia may lead to tertiary hyperparathyroidism in patients with malabsorption or renal disease,<sup>13,14</sup> while adrenal adenomas have been reported in Cushing's syndrome associated with a pituitary tumor.<sup>15</sup> One possible example of tertiary hyperaldosteronism has been described. This patient with renal disease and a documented high plasma renin value on one occasion later developed aldosterone excess associated with low plasma renin<sup>16</sup> at operation hyperplasia of the zona glomerulosa but no adenoma was found.

The incidence of renal and renovascular disease in this series seems in general similar to that of large series from general hypertension clinics.<sup>7</sup> If primary hyperaldosteronism commonly resulted from prolonged adrenal stimulation secondary to renal or renovascular disease one might expect a higher incidence of such abnormalities than in the general hypertensive population. Because renal investigations and diagnostic criteria may vary between centers and because of possible selection bias we cannot exclude the possibility that renal disease may occasionally result in tertiary hyperaldosteronism; however it seems unlikely that this mechanism is common. It also seems unlikely that patients with adrenal hyperplasia represent an early stage in the pathogenesis of adrenal adenomas as in this series those with adenomas were significantly younger than those in whom a tumor was not found at operation.

**Table III** Classification of the adrenal changes in 65 patients of this series

| Group*                    | Histological subdivisions   | Nos |
|---------------------------|---|-----|
| 1 Adrenocortical tumor*   | Adrenal adenoma with hyperplasia of zona glomerulosa  | 20  |
|                           | Adrenal adenoma with hyperplasia of zona glomerulosa and with nodules                                     | 25  |
| 2 No adrenocortical tumor | Hyperplasia of zona glomerulosa   | 3   |
|                           | Hyperplasia of zona glomerulosa with micronodules   | 4   |
|                           | Hyperplasia of zona glomerulosa with micronodules and macronodules  | 8   |
|                           | Normal zona glomerulosa with micronodules   | 2   |
| 3 Uncertain pathology     | Either an adrenal adenoma or a macronodule hyperplasia of zona glomerulosa with micronodules also present | 3   |

An adrenocortical adenoma was reported in a further 17 patients in this series but tissue was not available for review

When patients with raised DOC values were compared with those with normal concentrations there was no significant difference in mean ages, there were seven and six females in the respective groups. There was no significant difference between the groups in mean plasma concentrations of aldosterone sodium potassium total  $CO_2$ , urea, renin or angiotensin II or in total exchangeable sodium potassium or total body water. Mean blood pressure before treatment was similar as was the blood pressure response to treatment with spironolactone and following appropriate adrenal surgery.

**Plasma 18 hydroxy 11 deoxycorticosterone (18 OH DOC)** Plasma 18 OH DOC was measured in 15 patients (20 estimations). Mean values ranged from 7.5 to 164 ng/100 ml (normal 10 to 50 ng/100 ml). A subnormal value was observed in two patients while in 5 others the value was variably raised (Fig 2).

**Plasma corticosterone** Plasma corticosterone was measured in 20 patients (25 estimations). Values ranged from 0.02 to 0.86  $\mu$ g per 100 ml (normal 0.08 to 0.8  $\mu$ g/100 ml). Values were marginally raised in two patients while a subnormal value was observed in another (Fig 2).

#### Correlations of total exchangeable sodium

Total exchangeable sodium was measured before treatment in 32 patients in the proved adenoma group and in nine in whom a tumor was not found at operation. Although the correlations reported here did not reach conventional levels of significance in the adenoma group there was a positive correlation between total exchangeable sodium and both systolic ( $r = 0.22$ ) and diastolic ( $r = 0.24$ ) blood pressure and with plasma aldosterone ( $r = 0.25$ ), while there was a negative correlation with plasma renin concentration ( $r = -0.26$ ). Such correlations would be expected if the hypertension in patients with an aldosterone producing adenoma is due to aldosterone induced sodium retention. However, in the non adenoma group these correlations did not hold and total exchangeable sodium correlated weakly but negatively with systolic ( $r = -0.08$ ) and diastolic ( $r = -0.18$ ) pressure and with plasma aldosterone ( $r = -0.79$ ), while exchangeable sodium correlated positively with plasma renin concentration ( $r = 0.35$ ).

**Plasma renin concentration and age** In patients with essential hypertension there is an inverse correlation between plasma renin concentration and age,<sup>12</sup> possibly the result of renal adaptation to prolonged elevation of blood pressure.<sup>13</sup>

A similar inverse correlation with age was observed among patients in the non adenoma group ( $r = -0.614$ ,  $p < 0.01$ ) but not among those in whom an adrenocortical adenoma was found ( $r = 0.129$ , NS).

#### Pathology

In this series patients were divided into three main groups, those in whom a unilateral adrenocortical adenoma was found, those in whom a tumor was not identified and a small group in whom the adrenal lesion proved difficult to classify.<sup>24, 25, 26, 27, 28</sup>

Adrenal tissue was obtained at operation in 79 cases and at autopsy in three. In 65 patients tissue was available for review and classification according to defined criteria<sup>11, 12</sup> and the findings are summarized in Table III (see also Figs 3 and 4). An adrenocortical adenoma was described in a further 17 patients but tissue was not subsequently available for review.

**Adrenocortical adenoma** The majority of tumors weighed less than 3 Gm and measured 2 cm or less in diameter. The adenoma was located in the left gland in 63 per cent. The pathology of

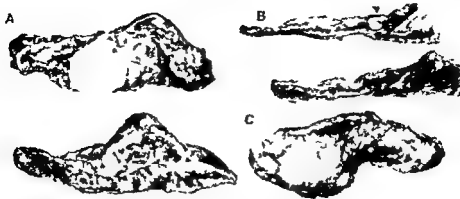


Fig 3 A B and C A An adrenal adenoma 1 cm in diameter is contained wholly within the gland which also contains small nodules B The adrenal gland removed from another patient with hyperaldosteronism weighed 5.0 Gm and shows a thinned cortex and several small nodules the largest 0.5 cm in diameter (arrow) C The adrenal gland removed at surgery contained a 1.0 by 0.35 by 0.5 cm yellow intraglandular lesion Histologically it contained only clear lipid laden cells In monolayer culture aldosterone production was demonstrated Hence the tumor is functionally an adrenal adenoma Electron microscopic sections were not available for study

system: Hyperaldosteronism in those patients in whom an adrenal tumor is not found might result from an unrecognized adrenal trophic stimulus. Nicholls and colleagues<sup>1</sup> recently described such trophic activity in a bioassay system using plasma from a single patient. These workers speculated that prolonged stimulation might result in the development of adrenal autonomy (a form of tertiary hyperaldosteronism).

Another possibility is that the hyperaldosteronism in non adenoma patients results in an unknown way from prolonged hypertension perhaps with eventual adrenal autonomy. Dobie described capsular arteriopathy in most adrenal glands with nodular hyperplasia and speculated that this small vessel disease might initiate focal hyperplasia. It is of interest that patients in this group show a significant inverse correlation between plasma renin concentration and age as is found in essential hypertension. In contrast such a correlation was not found among patients with aldosterone producing adenomas.

**Pathology** The characteristics of an aldosterone producing adenoma have been discussed.<sup>1</sup> Such tumors have a golden yellow cut surface and may project from the gland or be wholly intraglandular (Fig 3). With increasing size areas of necrosis hemorrhage and cystic change can occur. On light microscopy such tumors may be composed of four cell types: zona glomerulosa type cells, zona reticularis type (compact) cell, and large and small hybrid cells

(cells with some features of glomerulosa cells and some of fasciculata cells). However few adenomas consist of one cell type only and all four types can occur in one tumor.

Using non proliferating monolayer cultures it has recently been shown that zona glomerulosa type cells and both large and small hybrid cells can all produce aldosterone, corticosterone and cortisol.<sup>12</sup> However it is still not clear whether aldosterone producing tumors combine the functional features of both zona glomerulosa and zona fasciculata cells or consist functionally only of zona glomerulosa type cells. Electron microscopic observations of both the large and small hybrid cells have indicated that they possess mitochondrial agranular endoplasmic reticulum and plasmalemmal features similar to those of zona glomerulosa and not of zona fasciculata cells.<sup>13,14</sup>

In the normal adult adrenal cortex the aldosterone producing zona glomerulosa has a focal distribution around its periphery.<sup>1</sup> In primary hyperaldosteronism three different distributions of the zona glomerulosa may occur. It may be normal exhibit focal hyperplasia (of increased width but with focal distribution) or diffuse hyperplasia (present around the entire periphery of the cortex and of normal or increased width) (Fig 4). When hyperplasia is marked areas of the zona glomerulosa may extend into the cortex in a tongue like manner.

The adrenocortical nodules found in this condition have similar gross microscopic and ultra

**Biochemical features** Our results confirm and expand previous reports that the biochemical abnormalities in primary hyperaldosteronism are more severe among patients with an adrenocortical adenoma, compared with those in whom a tumor is not identified.<sup>23, 24, 26, 28</sup> Mean plasma concentrations of aldosterone, sodium and tCO were significantly higher, and mean concentrations of potassium and renin were significantly lower. Total exchangeable sodium was also higher and total exchangeable potassium lower, in the adenoma group.

As previously reported,<sup>22</sup> hypokalemia occurred in all patients with an adrenocortical adenoma and was usually persistent. However, among 17 in whom an adrenal tumor was not identified, hypokalemia was less severe and usually intermittent, while three examples of normokalemic primary hyperaldosteronism were found in this group.

Hypokalemia occurred in 89 per cent of patients in this series. However this does not indicate the true incidence of hypokalemia in primary hyperaldosteronism, as many patients were initially referred because of unexplained hypokalemia. Furthermore the incidence will, to an extent, be influenced by the number of potassium measurements made, and in some instances the diagnosis may be first suspected when diuretic induced hypokalemia occurs.<sup>17</sup> Conn<sup>16, 26</sup> has suggested that normokalemic primary hyperaldosteronism may be quite common in the hypertension population but others have failed to confirm this.<sup>27, 101</sup>

Although plasma aldosterone was elevated at least once in all cases, this abnormality was often intermittent.<sup>102</sup> For this reason measurements of potassium seem as sensitive as single measurements of plasma aldosterone in screening for this condition and are certainly more sensitive than single measurements of plasma renin concentration (Table II). This seems particularly so among patients with adrenocortical adenomas: hypokalemia was found in all and was persistent in 85 per cent, while plasma aldosterone was persistently raised in 71 per cent and renin was consistently suppressed in only 21 per cent.

**Other corticosteroids** Increased plasma levels of deoxycorticosterone (DOC) and corticosterone are not surprising, for these steroids are precursors of aldosterone<sup>103</sup> and their content is increased in adenomas associated with primary hyperaldosteronism.<sup>104, 106</sup> Plasma deoxycorticosterone

was raised in 50 per cent of patients and thus added abnormality was seen in both the adenoma and non adenoma groups. Biglieri and colleagues<sup>41</sup> reported that DOC secretion rates were raised in four of 14 patients with an aldosterone producing adenoma. Crane and Harris<sup>107</sup> reported increased DOC secretion in a patient with primary hyperaldosteronism associated with an adrenal carcinoma, while DOC secretion was normal in each of two with an aldosterone producing adenoma.

It seems unlikely that the raised values of DOC we report could result from ACTH stimulation by stress, as in most cases concurrent plasma cortisol levels were normal. Aldosterone is a much more potent mineralocorticoid than is DOC,<sup>108</sup> so it is not surprising that raised levels of DOC, in addition to aldosterone, did not further exacerbate the biochemical abnormalities.

Plasma corticosterone was marginally elevated in two of 20 patients. Plasma corticosterone (measured by a double isotope derivative technique<sup>41</sup>) was raised in one of 12 patients with primary hyperaldosteronism previously reported by Brown and associates in 1968<sup>11</sup> while Biglieri and colleagues<sup>41</sup> found a raised corticosterone secretion rate in seven of 17 patients with an aldosterone producing adenoma.

**Adenoma and non adenoma cases** The positive correlations between total exchangeable sodium and both systolic and diastolic blood pressure supports the concept that hypertension in patients with aldosterone producing adenomas is caused by sodium retention.<sup>109</sup> Because these correlations did not reach conventional levels of significance conclusions must be tentative; however such correlations were not seen in the non adenoma group suggesting another cause for the hypertension in these patients.

Aldosterone producing adenomas were commoner in females but such a sex difference was not observed in the non adenoma group. Patients with adenoma were also significantly younger. The fact that adenoma and non adenoma patients may be separated by statistical techniques such as quadratic analysis<sup>44</sup> also suggests that these groups are different entities rather than grades of the same disease.<sup>110</sup>

The combination of aldosterone excess and low plasma renin concentration is to be expected in any condition in which aldosterone secretion is stimulated other than by the renin-angiotensin

normal zona reticularis may be present. There is arteriopathy of the capsular adrenal vessels of all nodule bearing glands.

In vitro micronodules can form cortisol but not aldosterone while aldosterone can be extracted from adenomas but not from nodules.<sup>106, 113</sup> Electron microscopy has shown that the cells of nodules lack the structural characteristics of aldosterone forming cells.<sup>113</sup> Thus it seems that adrenocortical nodules may be an incidental finding in these patients and certainly are not an invariable feature (Table III).

Few pathological details have been reported by other workers of patients with primary hyperaldosteronism in whom a tumor was not found at operation. However the material reported by Wolff and colleagues<sup>1</sup> has been reviewed by one of us (A. M. N.) and changes similar to those found in the present series were seen: hyperplasia of the zona glomerulosa with micronodules being the most frequent finding.

While multiple tumors have been reported in some series, previous studies have not appreciated the possibility that a tumor together with macro and/or micronodules can occur in the same and/or opposite glands. This combination which was seen on several occasions in this present group might account for some of the reported examples of multiple or bilateral tumors.

Although not encountered in this series, hyperaldosteronism occurs rarely in association with adrenal carcinoma. The pathological features have been reviewed recently.<sup>114</sup> The different cellular patterns found in benign tumors also occur in carcinomas. Characteristically the cells are arranged in alveoli separated by prominent thick walled vascular sinusoids. Pleomorphism, mitotic activity, necrosis and hemorrhage may or may not be present.

### Summary

The clinical and biochemical findings in 136 patients with low renin (primary) hyperaldosteronism are described. A pathological diagnosis was made in 82 cases and a unilateral adrenocortical adenoma was found in 62. However a tumor was not identified in 17 of the adrenal glands then usually showing hyperplasia of the zona glomerulosa often with nodular changes. The adrenal lesion in a further three cases proved difficult to classify.

Patients with an adrenocortical adenoma were significantly younger than those in whom a

tumor was not found. The female/male ratio was greater than 2:1 in the adenoma group, but no sex difference was observed in the group without tumor. Vascular complications of hypertension occurred in 23 per cent and there was histologic evidence of malignant phase hypertension in four. It is concluded that this condition is not a benign form of hypertension.

Biochemical abnormalities were more marked among patients with an adrenocortical adenoma compared with those in whom a tumor was not found. Mean plasma concentrations of aldosterone, sodium and  $\text{CO}_2$  and mean exchangeable sodium were significantly higher while plasma potassium and renin concentrations and mean exchangeable potassium were significantly lower. Although plasma aldosterone was above normal at least once in all levels were often only intermittently raised. Hypokalemia occurred in all patients with a proved adenoma and was usually persistent. Among patients in whom a tumor was not found hypokalemia was less severe and usually intermittent, while plasma potassium was persistently normal in three of 17 patients in this group.

In addition to the aldosterone excess, plasma deoxycorticosterone was raised in 13 of 26 patients; plasma corticosterone was marginally raised in two and plasma 18 OH DOC in four of 16. There was a significant inverse correlation between plasma renin concentration and age in the non adenoma group but not among patients with an aldosterone producing adenoma. Weak positive correlations were observed in the adenoma group between total exchangeable sodium and both systolic and diastolic blood pressure and between exchangeable sodium and plasma aldosterone concentrations. Such correlations were not seen in the non tumor group. The hypertension may have a different basis in these two groups.

### REFERENCES

- Conn J. V. Primary aldosteronism: a new clinical syndrome. *J. Lab. Clin. Med.* 45:6, 1955.
- Conn J. W. and Conn J. S. Primary aldosteronism versus hypertensive disease with secondary aldosteronism. *Recent Prog. Horm. Res.* 17:389, 1961.
- Conn J. W. Primary aldosteronism. *J. Lab. Clin. Med.* 45:661, 1955.
- Conn J. W., Knopf R. F., and Nesbit R. M. Clinical characteristics of primary aldosteronism from an analysis of 145 cases. *Am. J. Surg.* 107:159, 1964.
- Luettscher J. A. Primary aldosteronism: observations in six cases and review of diagnostic procedures. *Medicine* 43:437, 1964.





Fig 4 A B and C A An adrenocortical adenoma is shown consisting of large and small "hybrid" cells. The cells form cords and acini; nuclear pleomorphism is present but not marked (Hematoxylin and eosin original magnification  $\times 160$ ). B Clear zona fasciculata like cells with small hyperchromatic regular nuclei comprise the nodule. The cells are grouped in cords and acini and are separated by fibrovascular trabeculae (Hematoxylin and eosin original magnification  $\times 300$ ). C A hyperplastic zona glomerulosa with tongues extending into the cortex is shown together with the associated prominent vascular spaces. The remainder of the cortex appears normal (Hematoxylin and eosin original magnification  $\times 120$ ).

structural features to those seen in Cushing's Syndrome and the so called "non functioning nodule" often found at autopsy.<sup>73</sup> Nodules visible to the naked eye are called macronodules while those seen only microscopically are termed

micronodules.<sup>74</sup> All are composed of clear lipid laden cells with light and electron microscopic features similar to the clear cells of the normal zona fasciculata. However, occasional nests of compact cells similar to those of the

44. Ehrlich, E. N. Dominguez, O. V. Samuels, L. T., Lynch, D. Oberhelman H. and Warner N. E. Aldosteronism and precocious puberty due to an ovarian androblastoma (Sertoli Cell tumor) *J Clin Endocrinol Metab* 23 358 1963
45. Todesco S. Terribile V. Borsatti A. and Mantero F. Primary aldosteronism due to a malignant ovarian tumor *J Clin Endocrinol Metab* 41 809 1975
46. Ferriss J. B. Beavers D. G. Brown J. J. Fraser R. Lever A. F., Padfield P. L., and Robertson J. I. S. Low renin (primary) hyperaldosteronism differential diagnosis and distinction of subgroups within the syndrome *AM HEART J* (In press)
47. Brown J. J. Davies D. L. Lever A. F. Peart W. S. and Robertson J. I. S. Plasma concentration of renin in a patient with Conn's Syndrome with fibrous lesions of the renal arterioles: the effect of treatment with spironolactone *J Endocrinol* 33 279 1965
48. Brown J. J. Ferriss J. B. Fraser R. Lever A. F. and Robertson J. I. S. Spironolactone in the treatment of hypertension with aldosterone excess. In: The medical uses of spironolactone G. M. Wilson ed Amsterdam 1971 *Excerpta Medica* p 27
49. Brown J. J. Davies D. L. Ferriss J. B. Fraser R. Haywood E. Lever A. F., and Robertson J. I. S. Comparison of surgery and prolonged spironolactone therapy in patients with hypertension aldosterone excess and low plasma renin *Br Med J* 2 729 1971
50. Ferriss J. B. Brown J. J. Fraser R. Haywood E., Davies, D. L. Kay A. W. Lever A. F., Robertson J. I. S. Owen K. and Peart W. S. Results of adrenal surgery in patients with hypertension aldosterone excess and low plasma renin concentration, *Br Med J* 1 135 1975
51. Beavers, D. G. Brown J. J. Ferriss J. B. Fraser R. Lever A. F. and Robertson J. I. S. The use of spironolactone in the diagnosis and the treatment of hypertension associated with mineralocorticoid excess *AM HEART J* 88 404 1973
52. Krenner D. Beavers D. G. Brown J. J. Davies, D. L. Ferriss, J. B. Fraser R. Lever A. F. and Robertson, J. I. S. Spironolactone and amiloride in the treatment of low renin hyperaldosteronism and related syndromes *Clin Sci Mol Med* 45 213s 1973
53. Padfield P. L., Allison M. E. H. Brown, J. J. Ferriss J. B. Fraser R. Lever A. F. Luke R. G. and Robertson J. I. S. Response of plasma aldosterone to fluid restriction in primary hyperaldosteronism and other forms of hypertension *Clin Endocrinol* 4 493 1975
54. Ferriss J. B. Beavers, D. G. Brown J. J. Fraser R., Krenner D. Lever A. F. and Robertson J. I. S. The treatment of low renin (primary) hyperaldosteronism *AM HEART J* (In press)
55. Bingham D. R. Robertson I., Robertson J. I. S. Robinson C. J. and Tree M. An interventional collaborative study of renin assay: establishment of the International Reference Preparation of Human Renin *Clin Sci Mol Med* 46 13s, 19 5
56. Brown J. J. Chinn H. H. Davies D. L. Fraser R. Lever A. F. Rae R. J. and Robertson J. I. S. Falsely high plasma potassium values in patients with hyperaldosteronism *Br Med J* 2 18 1970
57. Pickering, G. W. In *High Blood Pressure* 2nd ed London 1968, J & A Churchill, Ltd.
58. Brown, J. J. Davies, D. L., Lever A. F. Robertson J. I. S. and Tree M. The estimation of renin in human plasma *Biochem J* 111 534 1964
59. Tree M. Measurement of plasma renin-substrate in man *J Endocrinol* 56 153A 1973
60. Diusterdieck, G. and McEneaney G. Estimation of angiotensin II concentration in human plasma by radioimmunoassay. Some applications to physiological and clinical states *Eur J Clin Invest* 2 3\* 1971
61. Fraser R. and James V. H. T. Double isotope assay of aldosterone corticosterone and cortisol in human peripheral plasma *J Endocrinol* 40 59 1968
62. Fraser R. Guest S. and Young J. A comparison of double isotope derivative and radioimmunochemical estimation of plasma aldosterone concentration in man *Clin Sci Mol Med* 45 411 1973
63. Mason P. A. and Fraser R. Estimation of aldosterone 11-deoxycorticosterone 18 hydroxy 11-deoxycorticosterone corticosterone cortol and 11-deoxycortisol in human plasma by gas liquid chromatography with electron capture detection *J Endocrinol* 64 277 1975
64. Miller H. and Wilson G. M. The measurement of exchangeable sodium in man using the isotope  $^{22}\text{Na}$  *Clin Sci* 12 97 1953
65. Corsi L. Olney J. M., Steenberg R. W., Ball, M. R. and Moore F. D. The measurement of exchangeable potassium in man by isotope dilution *J Clin Invest* 29 1280 1950
66. Davies D. L. and Robertson J. W. K. Simultaneous measurement of total exchangeable potassium and sodium using  $\text{K}$  and  $\text{Na}$  Metabolism 22 133 19 3
67. Nicholson J. P. and Zilva J. F. Estimation of extra cellular fluid volume using Radiobromine *Clin Sci* 19 391 1960
68. Veall N. and Vetter H. Radiisotope techniques in clinical research and diagnosis London 1958 Butterworth & Co Ltd p 204
69. Veall N. and Vetter H. Radiisotope techniques in clinical research and diagnosis London, 1958 Butterworth & Co Ltd p 294
70. Atchison J. Brown J. J. Ferriss J. B. Fraser R. Hay A. W. Lever A. F. Neville A. M. Symington T., and Robertson J. I. S. Quadratic analysis in the preoperative distinction between patients with and without adrenal cortical tumors in hypertension with aldosterone excess and low plasma renin *AM HEART J* 82 660 1971
71. Beavers D. G. Brown J. J., Ferriss J. B. Fraser R. Lever A. F. Robertson J. I. S., and Tree M. Renal abnormalities and vascular complications in primary hyperaldosteronism. Evidence on tertiary hyperaldosteronism *Q J Med* 45 401 1976
72. Padfield P. L. Beavers D. G. Brown J. J. Davies D. L. Lever A. F. Robertson J. I. S. Schalekamp M. A. D. Tree M. and Titterton, M. Is low renin hypertension a stage in the development of essential hypertension or a diagnostic entity? *Lancet* 1 548 1975
73. Brown J. J. Lever A. F., Robertson J. I. S. and Schalekamp M. A. Renal abnormality of essential hypertension *Lancet* 2 390 1974
74. Symington T. Functional pathology of the human adrenal gland Edinburgh, 1969 E & S Livingston Ltd
75. Neville A. M. and Mackay A. M. The structure of the human adrenal cortex in health and disease *Clin Endocrinol Metabol* 1 381 1972
76. Brunner H. Laragh, J. H. Baer L. Newton M. A., Goodwin F. T. Krakoff L. R. Bard R. H. and Buhler F. R. Essential hypertension: renin and aldosterone heart attack and stroke *N Engl J Med* 286 441 1972
77. Schalekamp M. A. H. and Bukenhager W. H. Renin levels in hypertension *N Engl J Med* 286 1319 1972
78. Goldby F. S. and Beilin L. J. New thoughts on essential hypertension, *Br Med J* 2 591 1979

- 6 Conn J W Cohen E L Rovner D R and Nesbit R M Normokalemic primary aldosteronism: a detectable cause of curable essential hypertension *J A M A* 193 200 1965
- 7 Conn J W Rovner D R Cohen E L and Nesbit R M Normokalemic primary aldosteronism: its masquerade as essential hypertension *J A M A* 195 21 1966
- 8 Brown J J Davies D L Lever A F and Robertson J I S Plasma renin in hypertension Boerhaave course Hypertension Ed J de Graeff Leyden 1963 Leyden University p 44
- 9 Brown J J Davies D L Lever A F, Peart W S and Robertson J I S Plasma renin in a case of Conn's Syndrome with fibrinoid lesions: use of spironolactone in treatment *Br Med J* 2 1636 1964
- 10 Kirkendall W M Fitz A and Armstrong M L Symposium on hypertension hypokalemia and the diagnosis of hypertension *Dis Chest* 45 337 1964
- 11 Conn J W Cohen E L and Rovner D R Suppressed plasma renin activity in primary aldosteronism *J A M A* 190 213 1964
- 12 Brown J J Davies D L Lever A F and Robertson J I S Plasma renin concentration in human hypertension II: renin in relation to aetiology *Br Med J* 2 1215 1965
- 13 Barraclough M A Bacchus B Brown J J Davies D L Lever A F and Robertson J I S Plasma renin and aldosterone secretion in hypertensive patients with renal or renal artery lesions *Lancet* 2 1310 1965
- 14 Helmer O M Renin activity in blood from patients with hypertension *Can Med Assoc J* 90 221 1964
- 15 Fasciolo J C de Vito E Romero J C and Cucchi J N The renin content of the blood of humans and dogs under several conditions *Can Med Assoc J* 90 206 1964
- 16 Conn J W The evolution of primary aldosteronism 1954 1967 *Harvey Lect* 62 257 1968
- 17 Brown J J Chinn R H Davies D L Dusterdeck G Fraser R Lever A F Robertson J I S Tree M and Wiseman A Plasma electrolytes renin and aldosterone in the diagnosis of primary hyperaldosteronism with a note on plasma corticosterone concentration *Lancet* 2 55 1968
- 18 Davis W W Newsome H H Wright L D Hammond W G Easton J and Barter F C Bilateral adrenal hyperplasia as a cause of primary aldosteronism with hypertension hypokalemia and suppressed renin activity *Am J Med* 42 642 1967
- 19 Katz F H Primary aldosteronism with suppressed plasma renin activity due to bilateral nodular adrenocortical hyperplasia *Ann Intern Med* 67 1035 1967
- 20 Laragh J H Ledingham J G G and Sommers E C Secondary aldosteronism and reduced plasma renin in hypertensive disease *Trans Assoc Am Physicians* 80 168 1967
- 21 Grim C E McBryde A C Glenn J F and Gunnells J C Childhood primary aldosteronism with bilateral adrenocortical hyperplasia: plasma renin activity as an aid to diagnosis *J Pediatr* 71 377 1967
- 22 Rhamy R K McCoy R M Scott H W Fishman L M Mikellakis A M and Liddle G W Primary aldosteronism: experience with current diagnostic criteria and surgical treatment in fourteen patients *Ann Surg* 167 718 1968
- 23 Distler A, Barth C Roscher S Vecsei P, Dhoni G and Wolff H P Hochdruck und aldosteronismus bei isolierten adenomen und bei nodularer hyperplasie der nebennierenrinde *Klin Wochenschr* 47 688 1969
- 24 Ferriss J B Brown J J Fraser R Kay A W Lever A F Neville A M O'Murcheartaigh I M Robertson J I S and Symington T Hypertension aldosterone excess and low plasma renin: pre operative distinction between patients with and without adrenocortical tumour, *Lancet* 2 995 1970
- 25 George J M Wright L Bell N H and Barter F C The syndrome of primary aldosteronism *Am J Med* 48 343 1970
- 26 Baer L Sommers S C Krakoff L R Newton M A and Laragh J H Pseudo primary aldosteronism: an entity distinct from true primary aldosteronism *Circ Res* 26 and 27(Suppl 1) 203 1970
- 27 Biglieri E G Schambelan M Slaton P E and Stockigt J R The intercurrent hypertension of primary aldosteronism *Circ Res* 26 and 27(Suppl 1) 195 1970
- 28 Brown J J Chinn R H Dusterdeck G O Fraser R Gleadle R H Lever A F Robertson J I S and Tree M Hypertension and hyperaldosteronism with low plasma renin concentration: analysis of a series of 82 patients *Proc R Soc Med* 62 1258 1969
- 29 Nicholls M G Espiner E A Hughes H Ross Janne and Stewart D T Primary aldosteronism: a study in contrasts *Am J Med* 69 334 1975
- 30 Liddle G W In Discussion *Trans Assoc Am Physicians* 80 179 1967
- 31 Sutherland D J A Ruse J L and Lawlaw J C Hypertension increased aldosterone secretion and low plasma renin activity: relieved by dexamethasone *Can Med Assoc J* 95 1109 1966
- 32 New M I and Peterson R E A new form of congenital adrenal hyperplasia *J Clin Endocrinol Metab* 27 300 1967
- 33 Miura K Yoshinaga K Goto H Katsushima I Maebashi M Demura H Ino M Demura R and Tonkai T A case of glucocorticoid responsive hyperaldosteronism *J Clin Endocrinol Metab* 28 1807 1968
- 34 Giebink G S Gothin R W Biglieri E G and Katz F H A kindred with familial glucocorticoid suppressible aldosteronism *J Clin Endocrinol Metab* 36 115 1973
- 35 Foye L V and Feichtmeier T V Adrenal cortical carcinoma producing solely mineralocorticoid effect *Am J Med* 19 966 1955
- 36 Brooks R V McSwiney R R Prunty F T G and Wood F J Potassium deficiency of renal and adrenal origin *Am J Med* 23 391 1957
- 37 Zimmermann B Moran W H Rosenberg J C Kennedy W J and Frey R J Physiologic and surgical problems in the management of primary aldosteronism *Ann Surg* 150 653 1959
- 38 Crane M G Harris J J and Herber R Primary aldosteronism due to an adrenal carcinoma *Ann Intern Med* 63 494 1965
- 39 Neville A M and Symington T Pathology of primary aldosteronism *Cancer* 19 1854 1966
- 40 Harrison J H In Discussion *Ann Surg* 164 609 1966
- 41 Biglieri E G Slaton P E Schambelan M and Kronfeld S J Hypermineralocorticoidism *Am J Med* 45 170 1968
- 42 Altman S L Dominguez C, Lopez Gomez A. and Lieber A L Primary adrenocortical carcinoma causing aldosteronism *Cancer* 24 602 1969
- 43 Filipczak S, Felty Nowak T, Poplawski W, Lepinska K, Krus S Wocial II and Zaruszewicz W Carcinoma of the adrenal cortex with hyperaldosteronism *J Clin Endocrinol Metab* 35 22, 1972

## The hypertension complex

Milton Mendlowitz M.D.

New York N.Y.

Attention has been recently focused on hypertension because it is one of the most important underlying causes of vascular disease in the world and therefore a basic element in the process of aging and in death rate statistics. Since much hypertension is presumably remediable or at least controllable, we are often told that in order to prolong life there is public need to identify hypertension and treat it.

This simplistic approach ignores the complexities of the hypertensive process, possibly with some justification, but anyone working with hypertensive patients will certainly agree that an understanding of the underlying mechanisms and their development is of inestimable help in determining appropriate therapy for the individual patient.

Let us first consider the hereditary factor. There are several types of genetic abnormalities that result in hypertensive diseases. Pheochromocytoma is often hereditary and may be transmitted as an autosomal dominant trait. There are types of pheochromocytoma that occur in association with thyroid carcinoma, hyperparathyroid disease, and neurofibromatosis and submucous nodules which are very often hereditary and may be found in both adrenal glands or may even be multifocal. There is at least one type of hereditary chronic glomerulonephritis which is also probably transmitted as an autosomal dominant<sup>1</sup> and may be associated with hypertension. Polycystic kidneys often have an hereditary substrate and can cause hypertension as well as renal failure.

We must now consider the vast pool of hypertension labeled 'essential'. Many of these cases occur in families and most of us believe they have an hereditary substrate. The blood pressures aggregate in families even in childhood.<sup>2</sup> Stress hypertension is often lumped with essential hypertension and may be superimposed upon it. Stress hypertension which is largely environmentally produced, however, may exist alone or may even subside entirely.<sup>3</sup> It is not clear first whether essential hypertension is or is not fundamentally hereditary or merely familial, whether a genetic defect if present is in the central nervous system, sympathetic nervous system, blood vessels, tissues, electrolytes, endocrine glands or kidneys, and most of the evidence suggests that it is multi rather than uni-genic.

The most important type of developmental or congenital hypertension is exemplified by coarctation of the aorta, although it is conceivable that certain kinds of renovascular hypertension such as fibromuscular dysplasia may originate in this way.

What can we learn from acute hypertension that may help us in an understanding of the subacute and more chronic types? Let us first consider acute glomerulonephritis. Here salt and water is retained, blood volume is increased, cardiac output is increased and edema may be present but is often minimal. Plasma renin activity (PRA) is usually low or normal but may go up if fluids and sodium chloride are withheld. Sympathetic discharge if anything should be decreased because of the baroreceptor effects unless the sodium and water in the baroreceptor regions have blunted these reflexes. Not with holding sodium and water from the diet may result in increased hypertension with left ventricular failure and pulmonary edema even at levels of blood pressure that are only moderately

From the Department of Medicine, Mount Sinai School of Medicine, New York, N.Y.

Received for publication February 2, 1974

Reprint requests: Milton Mendlowitz, M.D., Dept. of Medicine, Mount Sinai School of Medicine, Fifth Ave. and 100th St., New York, N.Y. 10029

- 79 Doyle A E Jerums G Johnston C I and Louis W J Plasma renin levels and vascular complications in hypertension *Br Med J* 2 206 1973
- 80 Mroczek W J Finnerty F A and Catt K J Lack of association between plasma renin and history of heart attack or stroke in patients with essential hypertension *Lancet* 2 464 1973
- 81 Stroobandt R Fagard R and Amery A K P C Are patients with essential hypertension and low renin protected against stroke and heart attack? *Am Heart J* 86 781 1973
- 82 Pickering G W Hypertension causes consequences and management *Edinburgh and London 1974 Churchill Livingstone* p 74
- 83 Laragh J H Baer L Brunner H R Buhler F R Sealy J E and Vaughan E D Renin angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease *Am J Med* 52 633 1972
- 84 Kaplan N M Primary aldosteronism with malignant hypertension *N Engl J Med* 269 1282 1963
- 85 Del Greco F Dolkart R Skom J and Method H Association of accelerated (malignant) hypertension in a patient with primary aldosteronism *J Clin Endocrinol Metab* 28 808 1966
- 86 McAllister R G Van Way C W Dayan K Anderson W J Temple E Michelakakis A M Coppage W S and Oates J A Malignant hypertension effect of therapy on renin and aldosterone *Circ Res* 28 and 29 (Suppl II) 160 1971
- 87 Aloia J F and Beutou G Malignant hypertension with aldosterone producing adenoma *Am J Med Sci* 268 241 1974
- 88 Baxter R H and Wang I Malignant hypertension in a patient with Conn's syndrome *Scott Med J* 19 161 1974
- 89 Ross E J Aldosterone and aldosteronism *London 1975 Lloyd Luke* p 296
- 90 Stanbury S W and Mashler R F Salt wasting renal disease *Q J Med* 28 425 1959
- 91 Davies D R Dent C E and Watson L Tertiary hyperparathyroidism *Br Med J* 3 395 1968
- 92 Thomas W C and Fry R M Parathyroid adenomas in chronic neckties *Am J Med* 49 404 1970
- 93 Burke C W Doyle F H Joplin G F Arnot R N Macerlean D P and Fraser T R Cushing's disease *Q J Med* 42 693 1973
- 94 Luetscher J A Ganguly A Melada G A and Dowdy A J Pre operative differentiation of adrenal adenoma from idiopathic adrenal hyperplasia in primary aldosteronism *Circ Res* 34 and 35 (Suppl I) 175 1974
- 95 Ferriss J B Beevers D G Brown J J Fraser H Lever A F Robertson J I S and Wilson A Primary (low renin) hyperaldosteronism—progress report Proceedings of the Scottish Society for Experimental Medicine *Scott Med J* 20 334 1975
- 96 Conn J W Plasma renin activity in primary aldosteronism *J A M A* 190 222 1964
- 97 Ledingham J G G, Bull M B and Laragh J H The meaning of aldosteronism in hypertensive disease *Circ Res* 20 and 21 (Suppl II) 177 1967
- 98 Kaplan N M Hypokalemia in the hypertensive patient *Ann Intern Med* 66 1079 1967
- 99 Fishman L M Kuchel D Liddle G W Michelakakis A M Gordon R D and Chick W T Incidence of primary aldosteronism in uncomplicated essential hypertension *J A M A* 205 497 1968
- 100 Crane M G, Harris J J and Johns V J Hyporenemic hypertension *Am J Med* 52 457 1972
- 101 Beevers D G Nelson C S Padfield P L Barlow D H Duncan S Greaves D A, Hawthorne J M Morton J J Young G A R and Young J The prevalence of hypertension in an unselected population and the frequency of abnormalities of potassium angiotensin II and aldosterone in hypertensive subjects *Acta Clin Belg* 29 276 1974
- 102 Beevers D G Brown J J Fraser H Lever A F Robertson J I S Schalkamp M A D Semple P F and Wilson A Recent developments in the biochemical investigation of hypertension *Essays Med Biochem* 11 1975
- 103 Ayres P J Hechter O Saba N Simpson S A and Tait J F Intermediates in the biosynthesis of aldosterone by capsule strippings of ox adrenal gland *Biochem J* 65 22p 1957
- 104 Louis L H and Conn J W Content of aldosterone corticosterone hydrocortisone and cortisone in adrenal tissue of patients with primary aldosteronism *J Lab Clin Invest* 52 923 1958
- 105 Biglieri E G Hane H Slaton P E and Forsham P H In vivo and in vitro studies of adrenal secretions in Cushing's Syndrome and primary aldosteronism *J Clin Invest* 42 516 1963
- 106 Kaplan N M The steroid content of adrenal adenomas and measurements of aldosterone production in patients with essential hypertension and primary aldosteronism *J Clin Invest* 46 728 1967
- 107 Crane M G and Harris J J Deoxycorticosterone secretion rates in hyperadrenocorticism *J Clin Endocrinol Metab* 28 113j 1966
- 108 Muller A F Mach E and Naegeli H Comparison of the effect of aldosterone and cortisone (deoxycorticosterone) on electrolyte excretion in man *Acta Endocrinol* 20 113 1955
- 109 Davies D G Beevers D G Brown J J Fraser H Ferriss J B Lever A F Medina A Morton J J and Robertson J I S Sodium and the renin angiotensin system in patients with hypertension. Proceedings of the 4th International Congress of Endocrinology, Washington Amsterdam 1973 Excerpta Medica
- 110 Lever A F In Discussion *Circ Res* 28 and 29 (Suppl II) 190 1971
- 111 Dobbie J W Adrenocortical nodular hyperplasia the ageing adrenal *J Pathol* 111 1 1969
- 112 Hornsby P J O'Hare M J and Neville A M Functional and morphological observations on rat adrenal zona glomerulosa cells in monolayer culture *Endocrinology* 95 1240 1974
- 113 Mackay A M Atlas of human adrenal cortex ultrastructure in Functional pathology of the human adrenal gland by Symington T Edinburgh 1969 E & S Livingstone Ltd pp 346-489
- 114 Reddihall H and Fisher E R Aldosteronoma and non functioning adrenal cortical adenoma Comparative ultrastructural study *Arch Pathol* 68 155 1969
- 115 Vecsei P Furcz L and Wolff H P Studies on the biosynthesis of aldosterone in solitary adenoma and in nodular hyperplasia of the adrenal cortex in patients exhibiting Conn's Syndrome *Acta Endocrinol* 62 391 1969
- 116 Wolff H P Barth C Dastler A Dusterdieck G Kruck F, Roscher S Vecsei P and Weinger H F Hypokaliämischer und normokaliämischer primärer Aldosteronismus *Dtsch Med Wochenschr* 94 70 1969
- 117 Neville A M The pathology of tumours of the adrenal gland *Conso Superiore sui Tumori Delle Ghiandole Endocrine Ed Verona U* 297 Milan 1970 Casa Editrice

## The hypertension complex

Milton Mendlowitz MD

New York N Y

Attention has been recently focused on hypertension because it is one of the most important underlying causes of vascular disease in the world and therefore a basic element in the process of aging and in death rate statistics. Since much hypertension is presumably remediable or at least controllable we are often told that in order to prolong life there is public need to identify hypertension and treat it.

This simplistic approach ignores the complexities of the hypertensive process possibly with some justification but anyone working with hypertensive patients will certainly agree that an understanding of the underlying mechanisms and their development is of inestimable help in determining appropriate therapy for the individual patient.

Let us first consider the hereditary factor. There are several types of genetic abnormalities that result in hypertensive diseases. Pheochromocytoma is often hereditary and may be transmitted as an autosomal dominant trait.<sup>1</sup> There are types of pheochromocytoma that occur in association with thyroid carcinoma, hyperparathyroid disease and neurofibromatosis and submucous nodules which are very often hereditary and may be found in both adrenal glands or may even be multifocal. There is at least one type of hereditary chronic glomerulonephritis which is also probably transmitted as an autosomal dominant<sup>2</sup> and may be associated with hypertension. Polycystic kidneys often have an hereditary substrate and can cause hypertension as well as renal failure.

We must now consider the vast pool of hypertension labeled essential. Many of these cases occur in families and most of us believe they have an hereditary substrate. The blood pressures aggregate in families even in childhood.<sup>3</sup> Stress hypertension is often lumped with essential hypertension and may be superimposed upon it. Stress hypertension which is largely environmentally produced however may exist alone or may even subside entirely.<sup>4</sup> It is not clear first whether essential hypertension is or is not fundamentally hereditary or merely familial, whether a genetic defect if present is in the central nervous system, sympathetic nervous system, blood vessels, tissues, electrolytes, endocrine glands or kidneys and most of the evidence suggests that it is multi rather than uni-genic.

The most important type of developmental or congenital hypertension is exemplified by coarctation of the aorta although it is conceivable that certain kinds of renovascular hypertension such as fibromuscular dysplasia may originate in this way.

What can we learn from acute hypertension that may help us in an understanding of the subacute and more chronic types? Let us first consider acute glomerulonephritis. Here salt and water is retained, blood volume is increased, Cardiac output is increased and edema may be present but is often minimal. Plasma renin activity (PRA) is usually low or normal but may go up if fluids and sodium chloride are withheld. Sympathetic discharge if anything should be decreased because of the baroreceptor effects unless the sodium and water in the baroreceptor regions have blunted these reflexes. Not with holding sodium and water from the diet may result in increased hypertension with left ventricular failure and pulmonary edema even at levels of blood pressure that are only moderately

From the Department of Medicine, Mount Sinai School of Medicine, New York, N Y.

Received for publication February 11, 1977.

Reprint requests: Milton Mendlowitz, MD, Dept. of Medicine, Mount Sinai School of Medicine, Fifth Ave. and 100th St., New York, N Y 10029.

- 79 Doyle A E, Jerums G, Johnston C I and Lous W J Plasma renin levels and vascular complications in hypertension *Br Med J* 2 206 1973
- 80 Mroczek W J, Finnerty F A and Catt, K J Lack of association between plasma renin and history of heart attack or stroke in patients with essential hypertension *Lancet* 2 464 1973
- 81 Strobandt R, Fagard R and Amery A K P C Are patients with essential hypertension and low renin protected against stroke and heart attack? *AM HEART J* 86 781 1973
- 82 Pickering G W Hypertension causes consequences and management Edinburgh and London 1974 Churchill Livingstone p 74
- 83 Laragh J H, Baer L, Brunner H R, Buhler F R, Sealy J E and Vaughan E D Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease *Am J Med* 52 633 1972
- 84 Kaplan N M Primary aldosteronism with malignant hypertension *N Engl J Med* 269 1282 1963
- 85 Del Greco F, Dolkart R, Skom J and Method II Association of accelerated (malignant) hypertension in a patient with primary aldosteronism *J Clin Endocrinol Metab* 26 808 1966
- 86 McAllister R G, Van Way C W, Dayan K, Anderson W J, Temple E, Michelakis A M, Coppage W S and Oates J A Malignant hypertension effect of therapy on renin and aldosterone *Circ Res* 28 and 29 (Suppl II) 160 1971
- 87 Aloia J F and Beutow G Malignant hypertension with aldosterone producing adenoma *Am J Med Sci* 268 241 1974
- 88 Baxter H H and Wang I Malignant hypertension in a patient with Conn's syndrome *Scott Med J* 19 161 1974
- 89 Ross E J Aldosterone and aldosteronism London 1975 Lloyd Luke p 296
- 90 Stanbury S W and Mahler R F Salt wasting renal disease *Q J Med* 28 425 1959
- 91 Davies D R, Dent C E and Watson L Tertiary hyperparathyroidism *Br Med J* 3 395 1968
- 92 Thomas W C and Fry I M Parathyroid adenomas in chronic rickets *Am J Med* 49 404 1970
- 93 Burke C W, Doyle F H, Joplin G F, Arnot R N, Macerlean D P and Fraser T R Cushing's disease *Q J Med* 42 693 1973
- 94 Luetscher J A, Ganguly A, Melada G A and Dowdy A J Pre operative differentiation of adrenal adenoma from idiopathic adrenal hyperplasia in primary aldosteronism *Circ Res* 34 and 35 (Suppl I) 175 1974
- 95 Ferriss J B, Beavers D G, Brown J J, Fraser R, Lever A F, Robertson J I S and Wilson A Primary (low renin) hyperaldosteronism—progress report Proceedings of the Scottish Society for Experimental Medicine *Scott Med J* 20 334 1975
- 96 Conn J W Plasma renin activity in primary aldosteronism *J A M A* 190 222 1964
- 97 Ledingham J G G, Bull M E and Laragh J H The meaning of aldosteronism in hypertensive disease *Circ Res* 20 and 21 (Suppl II) 177 1967
- 98 Kaplan N M Hypokalemia in the hypertensive patient *Ann Intern Med* 66 1079 1967
- 99 Fishman L M., Kuchel O, Liddle G W, Michelakis A M, Gordon R D., and Chuck W T Incidence of primary aldosteronism in uncomplicated "essential" hypertension *J A M A* 205 497 1968
- 100 Crane M G., Harris J J and Johns, V J Hyporeninemic hypertension *Am J Med* 52 457 1972
- 101 Beavers D G, Nelson C S, Padfield P L, Barlow D H, Duncan S, Greaves, D A, Hawthorne V W, Morton J J, Young G A R and Young J The prevalence of hypertension in an unselected population, and the frequency of abnormalities of potassium, angiotensin II and aldosterone in hypertensive subjects *Acta Clin Belg* 29 276 1974
- 102 Beavers D G, Brown J J, Fraser R, Kremer H, Lever A F, Morton J J, Robertson J I S, Schalkamp M A D, Semple P F and Wilson A Recent developments in the biochemical investigation of hypertension *Essays Med Biochem* 11 1975
- 103 Ayres P J, Hechter O, Saba N, Simpson S A and Tait J F Intermediates in the biosynthesis of aldosterone by capsule strippings of ox adrenal gland *Biochem J* 65 22p 1957
- 104 Louis L H and Conn J W Content of aldosterone, corticosterone, hydrocortisone and cortisone in adrenal tissue of patients with primary aldosteronism *J Lab Clin Invest* 52 923 1958
- 105 Biglieri E G, Hane S, Slaton P E and Forham, P H In vivo and in vitro studies of adrenal secretions in Cushing's Syndrome and primary aldosteronism *J Clin Invest* 42 516 1963
- 106 Kaplan N M The steroid content of adrenal adenomas and measurements of aldosterone production in patients with essential hypertension and primary aldosteronism *J Clin Invest* 46 728 1967
- 107 Crane M G and Harris J J Deoxycorticosterone secretion rates in hyperadrenocorticism *J Clin Endocrinol Metab* 28 1135 1968
- 108 Muller A F, Mach E and Naegeli H Comparison of the effect of aldosterone and cortisone (deoxycorticosterone) on electrolyte excretion in man *Acta Endocrinol* 20 113 1955
- 109 Davies D L, Beavers D G, Brown J J, Fraser R, Ferriss J B, Lever A F, Medina A, Morton J J and Robertson J I S Sodium and the renin-angiotensin system in patients with hypertension Proceedings of the 4th International Congress of Endocrinology Washington Amsterdam 1973 Excerpta Medica
- 110 Lever A F In Discussion *Circ Res* 28 and 29 (Suppl II) 190 1971
- 111 Dobbie J W Adrenocortical nodular hyperplasia: the ageing adrenal *J Pathol* 99 1 1969
- 112 Hornsby P J, O'Hare M J and Neville A M Functional and morphological observations on rat adrenal zona glomerulosa cells in monolayer culture *Endocrinology* 95 1240 1974
- 113 Mackay A M Atlas of human adrenal cortex ultrastructure in functional pathology of the human adrenal gland by Symington T Edinburgh 1969 F & S Livingstone Ltd pp 346-489
- 114 Reidbord H and Fisher E K Aldosteronoma: comparison functioning adrenal cortical adenoma. Comparative ultrastructural study *Arch Pathol* 88 153 1969
- 115 Vecsei P., Purjesz I and Wolff H P Studies on the biosynthesis of aldosterone in solitary adenoma and in nodular hyperplasia of the adrenal cortex in patients exhibiting Conn's Syndrome *Acta Endocrinol* 62 331 1969
- 116 Wolff H P., Barth C, Distler A, Dusterdieck G., Kruck F., Roscher E, Vecsei, P and Weinges K F Hypokaliämischer und normokaliämischer primärer Aldosteronismus *Dtsch Med Wochenschr* 94 760 1969
- 117 Neville A M The pathology of tumours of the adrenal gland *Corso Superiore sui Tumori Delle Ghiandole Endocrine Ed Verona U. 20* Milan 1970 Casa Editrice

many normotensive subjects have blood pressures which rise or fall in response to environmental stimuli. The degree of lability however can be roughly measured and is related more to the secretion of and response to epinephrine rather than norepinephrine. Increased lability may or may not be the harbinger of more fixed essential hypertension. It can exist by itself in the young and into middle age and it may even be transient. What is more essential hypertension and certainly renal hypertension may be relatively fixed with little lability even from the beginning. Essential hypertension itself however tends to be more labile at its onset and to then become relatively more stable although higher especially when the kidneys become involved as manifested by nephrosclerosis.<sup>1</sup> Labile hypertension may also have its onset in the more elderly patient and may be associated with the effect of arteriosclerosis on the baroreceptors.<sup>2</sup> The systolic hypertension in the elderly caused by relative rigidity of the aorta and large blood vessels is also well known and thus and the decreased sensitivity of the baroreceptors may exist together. In the elderly one must also consider the possibility of renal artery stenosis due to atherosclerosis as a possible cause for the hypertension.<sup>3</sup>

Although lability of blood pressure should be clearly distinguished from paroxysms of hypertension this is impractical. A paroxysm of hypertension lasts for a few hours usually and then is followed by normal blood pressure for many hours and even for days. It can be highly suggestive of pheochromocytoma but can occur as a stress phenomenon alone. Also some pheochromocytoma can be associated with labile and even fixed hypertension or sometimes with normal blood pressure and therefore should be tested for widely since it is usually surgically curable. Untreated a pheochromocytoma can subject the patient to high mortality risk if general anesthesia is required for incidental surgery or delivery of a baby.<sup>4</sup>

Chronic hypertension has most often progressed in the course of the onset and development of essential hypertension but may involve other mechanisms as well. It can occur for example because of sodium retention in primary aldosteronism of the adrenal cortex. It can also occur as part of Cushing's syndrome due to it is believed to increased responsiveness to catecholamines.<sup>5</sup>

and also because of increased renin substrate and hence increased elaboration of angiotensin II.<sup>6</sup> Chronic hypertension can also be caused by hyperreninemia either because of severe nephrosclerosis major renal arterial stenosis or juxta glomerular cell tumor.<sup>7</sup> The major renal artery stenosis in turn may be caused by atheromatosis fibromuscular dysplasia or renal artery aneurysm and occasionally by tumor compression as by a pheochromocytoma or a malignant tumor of various origin. Chronic hypertension can also be caused by chronic renal disease such as glomerulonephritis pyelonephritis polycystic kidneys amyloidosis lupus nephritis etc. Another cause of chronic hypertension especially in the upper part of the body is coarctation of the aorta. To keep things in perspective however it should be mentioned that the bulk of chronic hypertensives fall into the essential category.

The onset of chronic essential hypertension is probably in one way or another related to the catecholamines. It is characterized by increased response to and secretion of epinephrine if there is a labile factor and an increased response to norepinephrine as a constant and persistent feature.<sup>8</sup> If the hypertension is of renal origin however no matter how chronic or severe the increased response to norepinephrine may be absent in more than 50 per cent of the cases.<sup>9</sup> The presence of increased norepinephrine reactivity in such cases therefore suggests underlying essential hypertension predisposing to the renal disease or coincidental in many cases because of the tremendous prevalence of essential hypertension.

As has been already pointed out however the way in which the catecholamines are involved is still quite obscure. It is known for example that in both normotensive and hypertensive subjects catecholamine release increases with age probably because of progressive stiffness of the walls of the baroreceptors with decreased sensitivity despite increased threshold and hence less inhibition of firing through the adrenergic sympathetic nerve complexes. We also know that more released catecholamines reach vascular and cardiac receptors and less return to the neural network in essential hypertension than in normotensive subjects,<sup>10</sup> but we do not know how much of this is attributable to simple hypertrophy of the blood vessel walls and how much is part of a basic chemical defect. The role of epinephrine is



increased. The left ventricle is not adapted to the increased load of increased cardiac output and either increased or inappropriately normal peripheral resistance. The left ventricle therefore fails. It is obvious here that salt and water retention up to a point can produce hypertension and this is true of other hypertensive states as well. If one feeds excess salt and water to a normal person or animal, hypertension is prevented only because of the kidneys' ability to excrete the excess. Even so, in some animals, moderate hypertension can be produced by feeding excess salt and water for a long period.<sup>8</sup>

When glomerulonephritis becomes sub acute, however, and we are faced with the nephrotic syndrome several things happen to reduce the blood pressure, often to normal levels despite high PRA. First, the low plasma proteins and anemia reduce blood viscosity although the anemia increases cardiac output. Second the excess sodium and water is now in the extracellular spaces and the sodium is not concentrated near the blood vessels where it can produce vasoconstriction by a variety of effects. Some of these effects are blood vessel wall edema<sup>9</sup> and inhibition of re uptake of catecholamines.<sup>7</sup> The blood vessel receptors may become refractory to circulating angiotensin II as well as to norepinephrine, both of which may leak into the intercellular fluid. It is interesting that high plasma renin activity is also found in cirrhosis of the liver with ascites, despite normal blood pressure probably due to the same mechanisms. In the syndrome reported by Bartter and associates<sup>9</sup> (high PRA, juxtaglomerular cell hypertrophy, high aldosterone, normal blood pressure, low serum potassium and normal sodium), the difficulty seems to be an excess of prostaglandin A or E since indomethacin can reverse the process.

There is another type of acute hypertension which is produced by increased vasoconstriction with or without increased cardiac output. This occurs, for example, in a clinical situation in which there is an acute increase in intracerebral pressure as in acute subdural hematoma, acute urinary tract obstruction, or iatrogenically, if one infuses angiotensin or arterenol or in so called stress hypertension occasioned by acute anxiety, or during a paroxysm of hypertension in a patient with pheochromocytoma or in an animal in which one has produced renovascular obstruction acutely. The cause of such hypertension is usually the

release into the blood stream or the release locally from autonomic nerve endings of such vasoactive substances as epinephrine, norepinephrine and angiotensin II and perhaps others not yet clearly identified. These substances stimulate vascular and cardiac receptors which in turn affect the adenylylase, 3, 5, AMP or 3, 5, GMP, and phosphorylase systems,<sup>9</sup> producing increased smooth and cardiac muscle contraction, as a rule or in the case of epinephrine, increased heart rate and cardiac output at certain dose levels and increased vasoconstriction at higher levels.<sup>10</sup> These are not simple reactions but are rather complex interactions, the increased pressure, for example, tending to be modified by an opposite effect via the baroreceptors.<sup>11</sup> The prostaglandins are also modifying substances,<sup>12</sup> and various other hormones may be involved temporarily. If the reaction is severe myocardial blood vessels and the heart itself may be affected and acute ventricular failure may be the result of such a process as well, because of the acutely increased load on the left ventricle unprepared by previous hypertrophy. Again, blood pressure levels as low as 180/100 or higher ones may produce this effect in the damaged but not hypertrophied heart.

In chronic hypertension whether essential or renal, the mechanisms are considerably more complex and therefore less well explored and understood. The first question to ask is how is the hypertension initiated, and the answer is often an indication merely of the prejudices of the one answering. My answer will also involve prejudice as well as prolonged observation and some experimental data.

Hypertension is extremely difficult to evaluate in childhood. First of all the blood pressure normally is lower as one descends the scale of years into childhood and infancy. Secondly the stress of blood pressure taking itself is greater in the child than in the adult and particularly in the infant. Fluctuations are therefore greater and trends are difficult to evaluate. It is of interest that blood pressure levels tend to aggregate in families and to be high in so called hypertensive families. There is little doubt, however, that most essential hypertension is of genetic origin and that the defect must therefore be present from birth but can only be made manifest by environmental stimulation.<sup>13</sup>

It might be pertinent now to discuss stability of blood pressure. All hypertensive patients and

substances including angiotensin II tend to leak into the fluid sumps and not reach vascular receptors. Also blood viscosity decreases because of anemia and hypoproteinemia although cardiac output may increase.

2 What about congestive heart failure? *Possible answer* There is increased peripheral resistance, but the cardiac output is usually decreased and therefore blood pressure may remain normal. If there is edema many of the mechanisms cited in paragraph 1 above may obtain.

3 Why is there often little hypertension in polycythemia vera where viscosity can often be doubled? *Possible answer* The cardiac output remains normal or low most of the blood being in venules and veins. Are the arterioles dilated or constricted? What is the effect of the increased available oxygen?

4 Why is the kidney so vulnerable in hypertension? *Possible answer* The glomeruli are the only capillaries between two arterioles and one of the kidney's chief functions is the regulation of fluid and electrolyte balance. The response of the kidneys to hypertension are therefore out of phase with the rest of the body in the direction of greater vasoconstriction.

5 Why is the brain so vulnerable? *Possible answer* Sympathetic responses of blood vessels of the cerebral tissue itself are relatively weak in comparison to skin, muscle, intestine or kidney. These cerebral vessels are therefore more likely to develop microaneurysms that lead to hemorrhage and edema as the blood pressure rises. The increased spinal fluid pressure on the other hand is an accelerating factor since it stimulates the vasomotor centers. The retina reflects events in the brain.

6 What is the role of the renal vasodilator substances such as prostaglandins, kinins, anti-renins and others? *Possible answer* A deficiency of these substances may contribute to essential hypertension but much more research is needed to delineate their exact role. The case of Bartter's syndrome suppressed by the prostaglandin inhibitor indomethacin is very provocative although the exact cause of the syndrome is still obscure.

7 What is the relationship of atherosclerosis to hypertension? *Possible answer* This is a complex question indeed. What is known is that hypertension is one of the factors that accelerates atherosclerosis although the latter may exist without

hypertension. Also atherosclerosis may increase hypertension in several ways. It can for example because of decreased elasticity increase systolic and decrease diastolic pressure. It can decrease the sensitivity of the baroreceptors and it can produce unilateral or bilateral renal artery stenosis. In the latter instances surgery is indicated especially if the PRA is increased in the affected renal vein or if the kidneys are very compromised and there are no other atherosclerotic risks. Also a trial of antihypertensive medical therapy is usually warranted in such cases. The situation is different in the younger patient especially with fibromuscular renal artery dysplasia. If the criteria delineated above are met the results of surgery are considerably better. Surgery may involve bypass of the stenosis, patch graft or rarely nephrectomy. If there is pre-existing essential hypertension or secondary nephrosclerosis of the opposite kidney the results of operation may only be moderate and antihypertensive drug therapy may still be required. Because of predisposition and incidence the combination of essential hypertension with atherosclerotic renal artery stenosis may be as high as 40 to 50 per cent.

### Therapy

To subject patients to mass therapy for hypertension to achieve epidemiological results is in my opinion absurd and doomed eventually to failure. In the first place there are patients who should not be treated at all and therefore medications can do them harm. This would include transient stress hypertension, some cases of early stress hypertension and some patients with remediable surgical conditions. Also no two patients can be treated alike for many reasons including sensitivities, stages of the disease, associated conditions, etc. Therefore this business of stepwise medication as prescribed in many journals and pharmaceutical company releases should be scrapped. In addition the therapy for hypertension is continually changing as new data and new drugs emerge. Each physician must be educated in all this and use his trained judgment in prescribing therapy. Nurse practitioners and aides can be trained in the same way by knowledgeable physicians if the load becomes too great.

As to specific drugs there is no law that states that every patient should be started with reserpine or with a diuretic. Reserpine itself is almost

not at all clear and it is not known whether epinephrine hyperreactivity can evolve into nor epinephrine hyperreactivity, or whether these are two separate processes which may exist together or separately. There is now evidence from dose-response curves that hyperreactivity to norepinephrine consists not only of the effect of smooth muscle hypertrophy but also of an intrinsic hypersensitivity to the neural hormones, but we do not know the significance of this.<sup>2</sup>

Let us now consider so called secondary factors which it must be admitted, may come to dominate the hypertension in various stages of the disease. Some of these have been studied extensively and some are relatively poorly understood. Let us first consider electrolyte and fluid balance together with the renin-angiotensin-aldosterone systems.<sup>21-24</sup> The organism has developed many safeguards to insure proper fluid and electrolyte homeostasis. If the blood pressure begins to rise for any reason these mechanisms come into play. The state of sodium and water equilibrium is generally reciprocal to the renin-angiotensin system and its cascades. If the initial increase in blood pressure causes increase in glomerular filtration and loss of electrolytes and water, particularly sodium, the renin-angiotensin system will come into play to retain these substances. There is also a balance between the renin-angiotensin system which stimulates aldosterone to retain sodium and aldosterone itself or its effects on the electrolytes which tend in turn, then, to inhibit the renin-angiotensin system. There is therefore always a balance between the two systems which may be tipped in either direction producing hyperreninemia and severe hypertension on the one hand or pseudohyperaldosteronism with sodium and fluid retention, potassium loss, and hypertension on the other. Aldosteronoma or a tumor of the juxtaglomerular apparatus is probably autonomous and not at all, or less, influenced by the factors discussed above. Their effects and end results, however, are similar. In both the latter instances surgery is usually necessary whereas this is not the case when the conditions are not autonomous.

There are other endocrine conditions including tumors that are related to hypertension and their mechanisms often differ. In Cushing's syndrome for example, the glucocorticosteroids produce an increase in renin substrate<sup>25</sup> as well as in vascular reactivity<sup>26</sup> to vasoactive substances

thus producing hypertension. In hyperparathyroidism, hypertension may be produced by the effect of increased available calcium on the kidney and vascular smooth muscle.<sup>27</sup> In hyperthyroidism the increased cardiac output may be associated with mild hypertension<sup>28</sup> but in myxedema, hypertension may be caused by increased production of and sensitivity to catecholamines.<sup>29</sup> The reason for the high incidence of hypertension in diabetes mellitus and in gout as well as in acromegaly is not clearly understood. Hypertension can also be seen in children with dysautonomia (Riley Day syndrome) as they grow older.<sup>30</sup> In hyperviscosity syndromes, such as are seen sometimes in multiple myeloma etc. and in polycythemia vera, the hypertension is usually mild and can be caused by increased blood viscosity,<sup>31</sup> whereas in Gaisboeck's syndrome the polycythemia is caused by decreased plasma volume which in turn the result of the hypertensive condition itself.<sup>32</sup> As the hypertensive disease develops structural changes begin to take place, particularly in the heart and arterioles, and especially so in chronic essential hypertension. The left ventricle working against increased peripheral resistance, becomes hypertrophied and the septum bulges into the right ventricle. This process is reversible unless fibrosis has intervened because of subendocardial ischemia or coronary artery stenosis. Similarly the arteriolar muscle which must work harder to maintain the increased resistance so as not to flood the capillaries with fluid, also develops concentric hypertrophy with increasing layers of muscle and elastic tissue, all of which is reversible unless fibrosis intervenes, in which case the changes become less reversible. Necroses such as are seen in malignant hypertension and aneurysms such as are found in perianteritis nodosa are of course, reversible only by the production of extensive scarring. Intimal hypertrophy, thrombosis, and recanalization are integral effects of malignant hypertension and all these changes are accelerating factors in the disease.

Here are presented possible answers to several unanswered questions with respect to mechanisms.

1 Why is there often no hypertension in cirrhosis of the liver with ascites and edema and in other edematous states such as nephrotic syndrome where plasma renin activity can be very high? Possible answer: The vasoactive

substances including angiotensin II tend to leak into the fluid sumps and not reach vascular receptors. Also blood viscosity decreases because of anemia and hypoproteinemia although cardiac output may increase.

2 What about congestive heart failure? *Possible answer* There is increased peripheral resistance but the cardiac output is usually decreased and therefore blood pressure may remain normal. If there is edema many of the mechanisms cited in paragraph 1 above may obtain.

3 Why is there often little hypertension in polycythemia vera where viscosity can often be doubled? *Possible answer* The cardiac output remains normal or low most of the blood being in venules and veins. Are the arterioles dilated or constricted? What is the effect of the increased available oxygen?

4 Why is the kidney so vulnerable in hypertension? *Possible answer* The glomeruli are the only capillaries between two arterioles and one of the kidneys' chief functions is the regulation of fluid and electrolyte balance. The response of the kidneys to hypertension are therefore out of phase with the rest of the body in the direction of greater vasoconstriction.

5 Why is the brain so vulnerable? *Possible answer* Sympathetic responses of blood vessels of the cerebral tissue itself are relatively weak in comparison to skin, muscle, intestine or kidney. These cerebral vessels are therefore more likely to develop microaneurysms that lead to hemorrhage and edema as the blood pressure rises. The increased spinal fluid pressure on the other hand is an accelerating factor since it stimulates the vasomotor centers. The retina reflects events in the brain.

6 What is the role of the renal vasodilator substances such as prostaglandins, kinins, anti-renins and others? *Possible answer* A deficiency of these substances may contribute to essential hypertension but much more research is needed to delineate their exact role. The case of Bartter's syndrome suppressed by the prostaglandin inhibitor indomethacin, is very provocative although the exact cause of the syndrome is still obscure.

7 What is the relationship of atherosclerosis to hypertension? *Possible answer* This is a complex question indeed. What is known is that hypertension is one of the factors that accelerates atherosclerosis, although the latter may exist without

hypertension. Also atherosclerosis may increase hypertension in several ways. It can, for example, because of decreased elasticity, increase systolic and decrease diastolic pressure. It can decrease the sensitivity of the baroreceptors and it can produce unilateral or bilateral renal artery stenosis. In the latter instances surgery is indicated especially if the PRA is increased in the affected renal vein or if the kidneys are very compromised and there are no other atherosclerotic risks. Also a trial of antihypertensive medical therapy is usually warranted in such cases. The situation is different in the younger patient especially with fibromuscular renal artery dysplasia. If the criteria delineated above are met the results of surgery are considerably better. Surgery may involve bypass of the stenosis, patch graft or rarely nephrectomy. If there is pre-existing essential hypertension or secondary nephrosclerosis of the opposite kidney the results of operation may only be moderate and antihypertensive drug therapy may still be required. Because of predisposition and incidence the combination of essential hypertension with atherosclerotic renal artery stenosis may be as high as 40 to 50 per cent.

### Therapy

To subject patients to mass therapy for hypertension to achieve epidemiological results is in my opinion, absurd and doomed eventually to failure. In the first place there are patients who should not be treated at all and therefore medications can do them harm. This would include transient stress hypertension, some cases of early stress hypertension, and some patients with remediable surgical conditions. Also no two patients can be treated alike for many reasons including sensitivities, stages of the disease, associated conditions, etc. Therefore this business of stepwise medication as prescribed in many journals and pharmaceutical company releases should be scrapped. In addition the therapy for hypertension is continually changing as new data and new drugs emerge. Each physician must be educated in all this and use his trained judgment in prescribing therapy. Nurse practitioners and aides can be trained in the same way by knowledgeable physicians if the load becomes too great.

As to specific drugs there is no law that states that every patient should be started with reserpine or with a diuretic. Reserpine itself is almost

not at all clear and it is not known whether epinephrine hyperreactivity can evolve into nor epinephrine hyperreactivity or whether these are two separate processes which may exist together or separately. There is now evidence from dose-response curves that hyperreactivity to norepinephrine consists not only of the effect of smooth muscle hypertrophy but also of an intrinsic hypersensitivity to the neural hormones, but we do not know the significance of this.

Let us now consider so called secondary factors which it must be admitted may come to dominate the hypertension in various stages of the disease. Some of these have been studied extensively and some are relatively poorly understood. Let us first consider electrolyte and fluid balance together with the renin-angiotensin-aldosterone systems.<sup>3,4</sup> The organism has developed many safeguards to insure proper fluid and electrolyte homeostasis. If the blood pressure begins to rise for any reason these mechanisms come into play. The state of sodium and water equilibrium is generally reciprocal to the renin-angiotensin system and its cascades. If the initial increase in blood pressure causes increase in glomerular filtration and loss of electrolytes and water, particularly sodium, the renin-angiotensin system will come into play to retain these substances. There is also a balance between the renin-angiotensin system which stimulates aldosterone to retain sodium and aldosterone itself or its effects on the electrolytes which tend in turn then, to inhibit the renin-angiotensin system. There is therefore always a balance between the two systems which may be tipped in either direction producing hyperreninemia and severe hypertension on the one hand or pseudohyperaldosteronism with sodium and fluid retention, potassium loss, and hypertension on the other. Aldosteronoma or a tumor of the juxtaglomerular apparatus is probably autonomous and not at all or less influenced by the factors discussed above. Their effects and end results however are similar. In both the latter instances surgery is usually necessary, whereas this is not the case when the conditions are not autonomous.

There are other endocrine conditions including tumors that are related to hypertension, and their mechanisms often differ. In Cushing's syndrome, for example, the glucocorticosteroids produce an increase in renin substrate<sup>5</sup> as well as in vascular reactivity<sup>6</sup> to vasoactive substances

thus producing hypertension. In hyperparathyroidism, hypertension may be produced by the effect of increased available calcium on the kidney and vascular smooth muscle.<sup>7</sup> In hyperthyroidism the increased cardiac output may be associated with mild hypertension<sup>8</sup> but in myxedema, hypertension may be caused by increased production of and sensitivity to catecholamines.<sup>9</sup> The reason for the high incidence of hypertension in diabetes mellitus and in gout as well as in acromegaly is not clearly understood. Hypertension can also be seen in children with dysautonomia (Riley Day syndrome) as they grow older.<sup>10</sup> In hyperviscosity syndromes such as are seen sometimes in multiple myeloma etc. and in polycythemia vera, the hypertension is usually mild and can be caused by increased blood viscosity<sup>11</sup> whereas in Garboeck's syndrome the polycythemia is caused by decreased plasma volume which is in turn the result of the hypertensive condition itself.<sup>12</sup> As the hypertensive disease develops, structural changes begin to take place particularly in the heart and arterioles, and especially so in chronic essential hypertension. The left ventricle working against increased peripheral resistance becomes hypertrophied and the septum bulges into the right ventricle. This process is reversible unless fibrosis has intervened because of subendocardial ischemia or coronary artery stenosis. Similarly the arteriolar muscle which must work harder to maintain the increased resistance so as not to flood the capillaries with fluid also develops concentric hypertrophy with increasing layers of muscle and elastic tissue all of which is reversible unless fibrosis intervenes, in which case the changes become less reversible. Necroses such as are seen in malignant hypertension and aneurysms such as are found in periarteritis nodosa are of course reversible only by the production of extensive scarring. Intimal hypertrophy, thrombosis, and recanalization are integral effects of malignant hypertension and all these changes are accelerating factors in the disease.

Here are presented possible answers to several unanswered questions with respect to mechanisms.

1. Why is there often no hypertension in cirrhosis of the liver with ascites and edema and in other edematous states such as nephrotic syndrome where plasma renin activity can be very high? Possible answer: The vasoactive

- Gitlow S E Urinary tritium excretion after administration of tritium labeled epinephrine (HE) to normotensive and essential hypertensive subjects *Clin Res* 21 947 1973 (abstract)
- 15 Vlachakis N D Mendlowitz M and DeGuzi D Diminished baroreceptor sensitivity in elderly hypertensives Possible role of atherosclerosis *Atherosclerosis* 24 243 1976
  - 16 Poutasse E F Surgical treatment of renal hypertension Results in patients with occlusive disease of renal arteries *J Urol* 82 403 1959
  - 17 Morris G C Cooley D A Crawford E S Barry W B and DeBailey M E Renal revascularization for hypertension *Surgery* 48 95 1960
  - 18 Gitlow S E Mendlowitz M and Bertani L M Biochemical evaluation of pheochromocytomas A review of ten years experience *Am J Cardiol* 26 270 1970
  - 19 Mendlowitz M Nefzich N Weinreb H L and Gitlow S E The effect of prednisone and prednisolone on reactivity of the digital blood vessels to 1 norepinephrine in normotensive and hypertensive subjects *J Appl Physiol* 16 89 1961
  - 20 Krakoff L R Plasma renin substrate Measurement by radioimmunoassay of angiotensin I concentration in syndromes associated with steroid excess *J Clin Endocrinol Metab* 37 100 1973
  - 21 Hirose M Arakawa K Kikuchi M Kawasaki T, Omoto T Hato H and Nagayama T Primary reninism with renal hamartomatous alteration, *JAMA* 230 1288 1974
  - 22 Hollenberg N K, and Adams D F The renal circulation in hypertensive disease *Am J Med* 60 773 1976
  - 23 Laragh J H *Hypertension manual*, New York 1974 Dun Donnelly Publishing Corp
  - 24 Genest J and Korw E *Hypertension* 7<sup>th</sup> Berlin Heidelberg and New York 1972 Springer Verlag
  - 25 Williams R H *Textbook of endocrinology* Philadelphia London Toronto 1968 W B Saunders Co p 929
  - 26 Thompson W O Dickie L F, Morris E and Halkvitch The high incidence of hypertension in toxic goiter and in myxedema *Endocrinol* 15 265 1931
  - 27 Christensen N J Increased levels of plasma noradrenaline in hypothyroidism *J Clin Endocrinol Metab* 35 359 1972
  - 28 Gitlow S E Bertani L M Wolk E K, Li H L, and Dziedicz S W Excretion of catecholamine catabolites by children with familial dysautonomia *Pediatrics* 26 513 1970
  - 29 Mendlowitz M The effect of anemia and polycythemia on digital intravascular blood viscosity *J Clin Invest* 27 565 1948
  - 30 Chrysant, S G Frolich, E B Adamopoulos P H, et al. Pathophysiologic significance of "stress" on relative polycythemia in essential hypertension *Am J Cardiol* 37 1069 1976
  - 31 Margolius H S Geller R de Jong W, Pisano J J, and Sjoerdsma A Urinary kallikrein excretion in hypertension *Proceedings of the Council for High Blood Pressure Research-Hypertension XX* New York 1971 American Heart Association p 125

### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc P O Box 765 Schenectady N Y 12301 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale.

an obsolete drug since it produces serious depression in some patients and bleeding peptic ulcers in others. Other drugs are more efficient and less hazardous.

As for diuretics, the major virtue of the thiazides is that they are effective, cheap and available in many forms. They also, however, accentuate diabetes, produce gout and often cause gastrointestinal disturbances as well as skin rashes. In addition, the potassium loss they produce often requires potassium supplementation and hence more pills. Spironolactones, on the other hand, though perhaps less effective, are very benign and produce few such side actions. They may, however, cause breast hypertrophy in the male and menstrual disturbances in the female. Furosemide is another choice with almost though not quite the incidence of the side effects of the thiazides.

Methyldopa is often recommended as a second or third drug. It is not a very effective drug and requires constant vigilance against a positive Coombs test and possible hemolytic anemia. It may also produce, though rarely, severe hepatic damage. It does produce lower plasma renin activity.

One of the most effective drugs available is guanethidine. I have no objection to using it in mild hypertension provided the dose is carefully monitored. The postural hypotension frequently found, the frequent bowel movements and ejaculation curtailment are its chief side effects but are not very troublesome. Neither guanethidine nor methyldopa should be used without a diuretic in order to prevent the salt and water retention produced by the former drugs.

One of the most frequently used first drugs today is propranolol. It is good for the labile or adrenalin induced hypertensive patient and is very benign in the severe hypertensive, especially one with angina, heart failure and asthma are contraindications. The drug may then be supplemented either by an alpha blocking drug like phenoxylbenzamine, or by hydralazine or minoxidil or any one of the other direct acting drugs now marketed. These include prazosin and may include other not yet marketed vasodilating drugs acting directly to inhibit vascular smooth muscle contraction. The addition of a diuretic then produces normotension in most of these cases with little or no postural hypotension. The drugs most frequently used today for hyperten-

sive emergencies are diazoxide and sodium nitroprusside. These drugs are usually used in a hospital setting, however.

The most important thing to remember in treating hypertensive patients is to individualize according to history, stage of the disease, and underlying diagnosis. Also, one must begin slowly and make increments or additions gradually in accordance with the pharmacology of the drugs and the individuality of the patient.

## Summary

The complex of factors that operate in the genesis as well as the development of various types of hypertensive disease is discussed. Questions are asked and possible answers given to only a few of the unsolved problems of hypertension. The treatment of hypertension especially with drugs, is then discussed in the light of these complex mechanisms.

## REFERENCES

1. Sheps S G. *Phochromocytoma in cardiovascular disorders*. Albert N. Brest and John H. Moyer eds. Philadelphia 1968 F A Davis Company p 979.
2. Perkoff G T. *Hereditary chronic nephritis in Diseases of the Kidney*. M H Strauss and L G Welt eds. Boston 1971 Little Brown & Company p 1275.
3. Londe S, Bourgoignie J J, Robson A M and Goldring D. Hypertension in apparently normal children. *J Pediatr* 78: 669 1971.
4. Mendlowitz M. The catecholamines in essential hypertension and thyroid disease. In: Hypertension J. Gerst and O. Kuchel eds. (In press).
5. Meneely G F. The effect of salt and water and other electrolytes in hypertension. In: Hypertension J. Moyer ed. Philadelphia 1969 W B Saunders Company p 250.
6. Tobian L. The electrolytes of arterial wall in experimental renal hypertension. *Circ Res* 4: 671 1956.
7. Krakoff L R, de Champlain J and Axelrod J. Altered norepinephrine metabolism and storage in experimental hypertension. *Circulation* 38 (Suppl II) 165 1967.
8. Bartter F C, Pronove P G, Jr, MacCardle R C, and Diller E. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. *Am J Med* 33: 811 1962.
9. Robinson G H, Butcher R A and Sutherland F W. *Cyclic AMP*. New York and London 1971 Academic Press p 146.
10. Von Euler U. *Noradrenaline*. Springfield Illinois 1956 Charles C Thomas Publisher.
11. Heymans C and Neil F. *Reflexogenic areas of the cardiovascular system*. London 1958 J and A Churchill Ltd.
12. Hickler R B. The prostaglandins in Hypertension. *Mechanisms and management*. C. Orenti, K F Kim and J H Moyer eds. New York and London Grune & Stratton Inc 1973 p 671.
13. Mendlowitz M. *Systolic arterial hypertension*. Springfield Illinois 1974 Charles C Thomas Publisher.
14. De Guis D, Mendlowitz M, Viskochil D, and

Large collateral channels have also been observed in patients with ventricular hypertrophy,<sup>16</sup> anemia<sup>17</sup>, "cor pulmonale"<sup>18</sup> and emphysema<sup>19</sup>. Although the precise physicochemical factors determining this enlargement are unclear myocardial hypoxia would appear to be a common denominator.

Thus human myocardial collateral channels have the capacity to enlarge. However the chronicity of the above conditions associated with large caliber collaterals raises doubts about the possibility of enlargement as an acute adaptive mechanism. Analyzing autopsy material Fulton<sup>21</sup> observed the number of large scale coronary anastomoses increased as the duration of angina pectoris increased. He found that patients dying with a history of angina spanning less than three months had only a few large scale anastomoses and concluded that years were necessary for collateral enlargement to occur in man. Using histologic and radiologic techniques Jones<sup>22</sup> examined hearts of patients dying after myocardial infarction and determined that collaterals were not well developed for eight weeks after the acute event. Thus impression of depressingly slow collateral development however may not be correct. The case report of a young boy who sustained traumatic perforation of the right atrium and ventricle is pertinent.<sup>23</sup> During an uncomplicated operation the chambers were repaired. Several days later a continuous murmur was heard and cardiac catheterization nine days after the initial injury revealed a fistula between the right coronary artery and right atrium. Coronary angiography revealed retrograde opacification of the right coronary artery distal to the fistula via extensive intercoronary collaterals from the left anterior descending and circumflex arteries. Other observations support this initial report. Furthermore spasm of the right coronary artery around the catheter during injection of contrast medium in a patient with normal coronary arteries has produced opacification of numerous collateral vessels to the left circumflex artery. There is thus some evidence that sizeable collaterals are either already present or can form within days—a more promising prospect than the autopsy studies would have indicated.

**Functional effects.** Morphology however does not provide reliable estimates of function and the presence of collaterals that can enlarge acutely is not sufficient to prove their importance. Porter<sup>24</sup>

in 1901 wrote "The passage of a fine injection mass from one vascular area to another proves nothing concerning the possibility of the one area receiving its blood supply from the other." Thus a distinction between anatomic and functional end artery was being made. However simple observations have suggested that coronary collaterals do play a functionally important role. Numerous cases of total coronary obstruction without myocardial damage have been documented.<sup>25, 26, 27, 28, 29</sup> and Lesbre and colleagues<sup>30</sup> stated that 6 to 8 per cent of examined hearts with coronary occlusion had no evidence of tissue necrosis. In Baroldi's material<sup>31</sup> as many as 44 per cent of patients with one or more coronary artery obstructions did not have histologic evidence of myocardial necrosis. Carleton and Boyd<sup>32</sup> described the case of a young man with traumatic laceration of the left anterior descending coronary artery. Prior to ligation of both ends vigorous back bleeding from the distal portion was observed. Subsequent to ligation the patient developed no electrocardiographic evidence of infarction suggesting preformed collateral vessels were able to metabolically support the area formerly perfused by the left anterior descending artery.

Infarction size is frequently smaller than the perfusion area of the obstructed vessel.<sup>33, 34, 35</sup> Furthermore some patients develop myocardial necrosis in areas remote from those of a recently occluded vessel.<sup>36</sup> In these latter cases it is postulated that the primary vessel to the infarcted area had been occluded sometime in the past with the myocardium being supplied by collaterals originating from the more recently occluded vessel. These observations support the functional significance of coronary collaterals.

Attempts to evaluate collateral channels in other than postmortem specimens have yielded conflicting results. Matched populations with equally severe coronary occlusive disease and differing only in the presence or absence of collateral vessels have been studied. Whereas some investigators have concluded collaterals have no effect on left ventricular performance,<sup>37, 38</sup> regional ventricular contraction,<sup>39</sup> ability to exercise or prognosis,<sup>40, 41</sup> others have documented beneficial effects on left ventricular function and contraction patterns,<sup>42</sup> as well as survival.<sup>43</sup> Perhaps these studies err in the definition of the study groups. As stated by Schaper<sup>44</sup> and by



## The functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance collateral flow

Michael V Cohen, M D  
Bronx N Y

The collateral circulation, blood flowing in single or interconnecting systems of channels, is alternative to a major vascular conduit which has become non-functional. Thus a collateral channel is an initially unused pathway which is recruited only after failure of the original vessel to permit normal flows. Collateral vessels may be preformed, in which case there is immediate expansion and subsequent growth in response to the new stresses, or may be formed *de novo* where the potential for cellular transformation is preserved. Following coronary obstruction, blood supply to jeopardized myocardium must be delivered by collateral channels. Although alteration of myocardial metabolism may be important to the salvage of ischemic tissue, development of an adequate collateral supply is central to ultimate tissue survival.

### Human studies

**Anatomic demonstration** The importance of the collateral circulation to myocardial function in man continues to be questioned and until recently documentation of the presence of collaterals in normal human myocardium was uncertain. Although collaterals in the human heart were first described by Lower in 1671 the treatise by Cohnheim and von Schulthess-Rechberg<sup>1</sup> in 1881 labeled coronary arteries 'end arteries' because of the inability to demonstrate anastomoses between the three major coronary systems of the normal heart. These conclusions were refuted by Spalteholz<sup>2</sup> in 1907 who announced that connections between coronary arteries were indeed present. Other prominent anatomists quickly agreed.<sup>3-5</sup> However, in 1938 Schlesinger<sup>6</sup> described his technique for injecting coronary arteries with a colored lead agar mass producing radiographs and dissecting the vessels. He and his co-workers examined over 1,000 hearts in the ensuing 13 years,<sup>7-9</sup> and concluded that anastomoses existed in only 10 per cent of normal human hearts. Subsequent careful radiologic investigations with radiopaque<sup>10-11</sup> or bismuth oxychloride gelatin<sup>12</sup> lipoidal masses, latex injection studies<sup>13-14</sup> and vinylite casts<sup>15</sup> of the coronary tree all demonstrated numerous 200  $\mu$  anastomoses in practically 100 per cent of normal human hearts. Rodriguez and Robbins<sup>16</sup> repeated some of Schlesinger's work and determined that technical factors prevented Schlesinger from identifying collaterals in normal hearts. With minor modifications of the technique, they demonstrated collateral channels in all examined normal hearts. Thus collateral channels do exist in normal human myocardium.

From the Division of Cardiology, Department of Medicine, Montefiore Hospital and Medical Center and the Albert Einstein College of Medicine, Bronx, New York.

Received for publication Oct. 21, 1977.

Reprint requests: Michael V. Cohen, M.D., Division of Cardiology, Montefiore Hospital and Medical Center, 111 East 210 Street, Bronx, N.Y. 10467.

**Collateral enlargement** Enlargement of collateral conduits in man is an accepted observation. Anatomic-pathologic<sup>4, 5, 10-11</sup> and coronary angiographic<sup>17</sup> studies of patients with coronary obstructive disease have frequently revealed tortuous collaterals with diameters in excess of 1 mm. The presented data, however, do not indicate whether the enlargement occurs prophylactically or subsequent to a coronary occlusion. These anastomoses can also enlarge without the stimulus of a coronary occlusion or constriction.

demonstrated a direct relationship between collateral channels and infarct size. These investigators ligated the left anterior descending coronary artery in dogs and then touched the edges of distribution of the ligated vessel with a hot cautery. The size of the infarct was always much larger than that in animals with an isolated coronary ligation. The burns were small and caused no central infarction in control animals. Hence epicardial collaterals in the dog do serve to limit the extent of ischemia.

Eckstein's early work<sup>1</sup> demonstrated a significant relationship between collateral development and electrocardiographic manifestations of ischemia. Coronary ligation in pigs produced marked ischemic changes. Retrograde coronary flow was negligible and no collaterals could be identified by postmortem coronary injection of barium sulfate mass. On the other hand the electrocardiogram of dogs following abrupt coronary occlusion was much less abnormal. Retrograde coronary flow was much higher in this species and generally those animals with the highest flows had minimal ischemic abnormalities. Furthermore in one half of the canine hearts the barium suspension passed from one coronary system to the other via anastomotic channels. Schley and co-workers<sup>2</sup> have also demonstrated an inverse relationship between the magnitude of collateral development and the degree of ischemic electrocardiographic abnormalities following coronary occlusion. More recently Stephan and colleagues<sup>3</sup> monitored S T segment changes following coronary occlusion in the dog by doing epicardial mapping during right atrial pacing and before and after practolol infusion. Collateral vessels were identified by postmortem injection. For any given level of heart rate, left ventricular  $dP/dt$  or myocardial oxygen consumption, the magnitude of S T elevation was significantly less in the animals with more abundant collateral anastomoses.

Survival after acute coronary occlusion has also been correlated with the degree of collateral development. As noted previously, the mortality rate in pigs is much higher than that in dogs.<sup>1, 2</sup> Approximately two thirds of dogs survive for at least eight hours after acute coronary ligation.<sup>4</sup> Those dying prematurely have significantly fewer collateral anastomoses than those living for at least eight hours.<sup>4</sup> No dogs with poorly developed collaterals survived left circumflex occlusion,

whereas 96.3 per cent of animals with well developed collaterals survived the acute event. Interestingly, pigs will survive coronary occlusion if an initial 85 per cent stenosis is produced at least 12 days before occlusion.<sup>5</sup> At the time of sacrifice these animals have rich anastomotic networks. Garza and colleagues<sup>6</sup> have shown the electrical threshold for ventricular fibrillation in dogs following coronary ligation to be significantly higher in hearts with good collateral development.

**Effect on infarct size.** A quantitative relationship between collateral vessel development and the size of infarcts following coronary obstruction has been derived. There is a significant inverse relationship between the amount of blood flow to the ischemic myocardium following occlusion and the measured areas of the ultimate infarct at one to seven days after the initial event.<sup>7, 8</sup> This relationship was established in dogs with either abrupt or gradual coronary ligations.<sup>8</sup> In one study myocardial necrosis was observed only when endocardial blood flow was reduced by approximately 50 per cent.<sup>8</sup> Below this level the inverse relationship between flow and infarct size was linear. Thus preformed collaterals have the capacity to limit both myocardial ischemia and necrosis. However, therapeutic measures intended to salvage jeopardized myocardium during the acute phase of infarction must rely on collateral recruitment and potential expansion.

Following coronary stenosis and obstruction the development of a transanastomotic gradient results in collateral dilatation. This dilatation is accompanied by rupture of the internal elastic membrane.<sup>9</sup> An initial phase of rapid radial growth occurs where cellular material is used to produce further dilatation of seemingly maximally stretched vessels. Within 3 to 4 days the luminal diameter of the collateral vessel in the dog may increase more than tenfold.

Infarct size is quite different in groups of dogs with abrupt and gradual coronary occlusions. Solid emboli into the left anterior descending coronary artery produce infarcts averaging 20 per cent of the left ventricular cross sectional area, whereas hollow emboli which gradually thrombose over a five to ten hour period produce average infarct sizes of only 4 per cent, with half of the animals having no grossly detectable areas of necrosis.<sup>1</sup> The only apparent difference

Lavine and associates,<sup>34</sup> the degree of collateralization reflects the severity of the coronary obstructive disease. Therefore, patients with collateral networks may have had more intense ischemia to initiate their development, thus making comparison with patients without collaterals hazardous.

Collateral flow in man has been quantitated infrequently. Injection of radioisotopes into the exposed left ventricular myocardium<sup>35</sup> or into a saphenous vein bypass graft<sup>3</sup> or measurement of retrograde flow from a bypass graft attached to a proximally occluded coronary artery<sup>33</sup> can be done only at the time of left thoracotomy. Therefore, these measurements have limited value.

Thus studies in man have demonstrated the existence of a preformed collateral network in normal myocardium which has the capacity to enlarge and which appears to have a protective effect. However, the physiology of collateral development, the acute changes occurring in ischemic myocardium, the magnitude of their beneficial effect, and the extent to which they can be acutely affected by pharmacologic or mechanical interventions cannot easily be studied in human subjects. With experimental animals it has been possible to approach more closely the answer to the possible significance of the collateral circulation. Although results in the experimental animals cannot be directly applied to man, these experiments have helped us to better understand the role of the collateral vessel.

### Animal studies

**Anatomic demonstration.** The two most commonly used animal models are the pig and dog. The pig has three major coronary arteries supplying the left ventricular myocardium, a situation analogous to that in man.<sup>36</sup> The dog, however, has a small right coronary artery which supplies only the right ventricular free wall.<sup>37</sup> Collateral anastomoses have the same histology in all three species.<sup>38</sup> Canine collaterals are generally epicardial in location,<sup>39-41</sup> although endocardial connections do exist.<sup>42</sup> Man has numerous anastomoses throughout the myocardial wall, especially near the epicardial and endocardial surfaces.<sup>43-45</sup> The ratio of blood flow to the epicardial and endocardial halves of the left ventricular wall following coronary occlusion is similar in both primate and canine species. The pig, on the other hand, has only sparse endocar-

dial and endomural connections.<sup>46-48</sup> This natural difference between dog and pig serves to illustrate the significance of a collateral circulation. Following abrupt<sup>49</sup> or even more gradual coronary occlusion in the pig, the mortality rates near 100 per cent and survivors of gradual occlusion have large, transmural infarcts.<sup>50</sup> The dog survival rate, however, usually exceeds 67 per cent,<sup>40</sup> and only small areas of necrosis develop. The pig with its sparse collaterals is quite vulnerable to the adverse effects of deprivation of myocardial nutrition, whereas the numerous collateral channels in the dog protect the myocardium and the animal. Quantitation of collateral blood flow to ischemic areas confirms that pig collaterals deliver less than one fourth of the flow carried by canine channels.<sup>41, 51</sup>

**Functional effects.** Although visual demonstration of canine collateral anastomoses is not difficult, functional significance is not immediately apparent. Flow to acutely ischemic areas averages 10 to 30 per cent of normal levels,<sup>52</sup> and intravenous injections of either dye<sup>53</sup> fluorescein,<sup>54</sup> or P<sup>32</sup> erythrocytes<sup>55</sup> demonstrate obvious staining or radioactivity in the distal myocardial areas deprived of antegrade flow. Wiggers, however, believed that this blood flowing through the ischemic area must be too sluggish to serve a useful purpose. Paradoxical bulging of ischemic myocardium following coronary occlusion supports this conclusion.<sup>56</sup> However, these same ischemic areas can be observed to contract normally several weeks later, at a time when resting regional blood flow to areas distal to the occlusion has actually returned to the pre-occlusion level.<sup>57-59</sup> Thus dog-like man has collaterals which can enlarge and which are functional. But one must question whether these anastomotic vessels have any value immediately following coronary occlusion, and whether their development can be altered to provide additional protection to jeopardized myocardium.

As in man, canine coronary arteries can be occluded without production of necrosis,<sup>60</sup> while infarcts that do develop are smaller than the perfusion area of the ligated vessel.<sup>61</sup> Schaper and co-workers<sup>62</sup> have tried to quantitate this relationship and estimate that only one half of the perfusion area of the occluded left anterior descending coronary artery in dogs is infarcted. These results have recently been confirmed by Rivas and colleagues.<sup>63</sup> Bobb and associates<sup>64</sup>

substantially higher = 76 ± 4.8<sup>8-10</sup> The epicardium is in effect a border zone Attempts to decrease infarct size may be attempts to convert transmural to endocardial infarcts

### Potential therapeutic benefits

Removal of obstructions to antegrade flow more than 1 1/2 hours later does not result in the expected restoration of normal blood flow to the ischemic region<sup>11</sup> This no reflow phenomenon has been attributed to local edema with resulting compression of microvasculature<sup>12</sup> Although most apparent when flow restoration is attempted cellular edema occurs in ischemic tissue as well Therefore therapy directed at reduction of cellular edema and hence collateral compression would appear to be a potentially successful means of limiting myocardial ischemia The hyperosmotic agent mannitol has been administered to dogs with acute and chronic myocardial ischemia with resulting increases in collateral and total coronary blood flows and myocardial contractility and decreases in the magnitude of epicardial ST segment elevation and extent of myocardial necrosis<sup>13</sup> Although partial reversal of no reflow is undoubtedly part of the drug's beneficial effect a direct action on vascular smooth muscle may also be invoked because of mannitol's ability to enhance blood flow to normal myocardium

Another seemingly promising intervention would be increase of aortic diastolic pressure or coronary perfusion pressure Elevation of blood pressure in animals with acute coronary occlusion diminishes myocardial ischemia despite the theoretical adverse effects of increased afterload<sup>14</sup> Diastolic counterpulsation increases collateral blood flow<sup>15</sup> as well as the number of collaterals visualized by postmortem angiography In a recent study Watson and co-workers<sup>16</sup> observed that the combination of mannitol and counterpulsation increased collateral flow to acutely ischemic regions of the left ventricle more than either intervention alone

Although vasodilators may decrease coronary arterial resistance and increase coronary blood flow few have the ability to augment coronary collateral flow Furthermore dilatation of the distal coronary arterioles may produce small decreases in coronary perfusion pressure which in turn may cause actual diminution of collateral supply (coronary steal<sup>17</sup>) The nitrates how

ever have been shown to elicit primary dilatation of coronary collateral channels which persists many minutes after the arterioles have regained their vascular tone<sup>18,19</sup> This collateral dilatation with its associated augmented blood flow can relieve myocardial ischemia and restore near normal contractility to regions with impaired shortening<sup>20,21</sup> Thus collaterals have muscular walls which respond predictably to the proper pharmacologic agent Additional investigation will undoubtedly uncover other agents with specific effects on coronary collaterals which can then be used clinically

Many attempts to stimulate collateral development have been made but few have any potential therapeutic benefit However daily treadmill running does promote collateral growth in dogs with critical coronary stenoses<sup>22</sup> Therefore exercise may be an important part of the long range therapeutic regimen for patients with coronary artery disease

Thus animal experimentation has yielded definite evidence that collateral vessels are functional after an abrupt coronary occlusion Although they are usually unable to prevent infarction the anastomoses do limit the extent of the ischemic process and mortality Once functional the collateral vessel undergoes a tremendous histologic anatomic and physiologic transformation which greatly increases its significance as an alternate route of supply to the ischemic heart Stimulation of collateral flow has tremendous clinical significance and must represent one of the important goals of future investigation Application of the results of animal research must be applied cautiously to any clinical situation and new methods and techniques must be evaluated critically without bias However the results obtained in the experimental setting hold great promise If collateral enlargement and/or growth could be induced either before or immediately after coronary occlusion then the effects of this dreaded coronary event would be significantly attenuated

### REFERENCES

- 1 Cohnheim J, von Schultness-Rechberg A Ueber die Folgen der Kranzarterienverschliessung für das Herz, Arch Pathol. Anat 85 503 1881
- 2 Spalteholz W Die Coronararterien des Herzens Verh. Anat. Ges 21 141 1907
- 3 Cross L The blood supply to the heart in its anatomical and clinical aspects New York, 1971 Paul B Hoeber Inc p 77

between the groups was the initial period during which the hollow plugs were slowly becoming occluded. It is postulated that during the pre occlusion period collaterals were stimulated to enlarge so that much of the ischemic myocardium could be metabolically supported following total obstruction. In chronically instrumented dogs with gradually progressive coronary occlusions, changes in collateral indices including retrograde coronary flow and xenon clearance from the ischemic region support the assumption of increased collateral flow prior to complete obstruction.<sup>22</sup>

**Effect of time on development** Temporal changes in collateral flow following acute coronary obstruction have been investigated by multiple techniques. Alterations in xenon clearance and thermal conductivity in the ischemic region have been inconsistent. However Pasyk and co workers<sup>23</sup> have documented increases in the indices of collateral flow in instrumented dogs 20 to 31 hours following acute left circumflex artery obstruction. With flowmeters implanted around the distal portions of occluded vessels, Elliot and associates<sup>24</sup> were able to identify collateral flow patterns within six to eight hours following occlusion. The use of radioactive microspheres has permitted quantitation of regional myocardial blood flow to both endo and epicardium at various time intervals following coronary occlusion. Marcus and co workers<sup>25</sup> noted a doubling of endocardial and epicardial flow as early as five minutes after coronary occlusion, and a further flow increase at one hour. Rivas and colleagues<sup>26</sup> and Smith and co workers<sup>27</sup> also observed flow to be significantly increased at two hours, although this observation was not confirmed by others.<sup>28, 29</sup> Twenty four hours following occlusion, blood flow to the central ischemic tissue is approximately doubled (0.12 to 0.18 " 0.12 to 0.29, " 0.25 to 0.53 " ml/min/gm). This increase was observed in both epicardial and endocardial halves. Thus blood flow to ischemic areas can increase acutely. During the initial 24 hour period, both peripheral coronary pressure and retrograde flow from the ligated vessel increased and collateral conductance doubled.<sup>30</sup> Besides the increase in blood supply to the ischemic area there is also an internal redistribution. Schaper and Pasyk<sup>31</sup> and Hurzel and associates<sup>32</sup> measured flow to the infarcted endocardium and surviving overlying

epicardium and noted that flow in the latter appeared to increase at the expense of the former within the first hour following coronary occlusion. Tissue destined to become necrotic perhaps swells significantly, thus compressing collateral channels and initiating a flow redistribution.

**Spatial distribution in ischemic tissue** Other than temporal distribution of collateral flow, spatial distribution is of especial concern to those interested in attempting to attenuate the ravages of myocardial ischemia. Although the existence of a border zone of partially ischemic tissue surrounding a central core of deeply ischemic tissue has been claimed by some, others believe that the underperfused area is uniformly ischemic and surrounded by normal myocardium. Becker and co workers<sup>33</sup> have documented a tenfold drop in flow from a border zone to the center of the ischemic region with intermediate flows between the two. However, before sectioning the heart they failed to specifically identify the ischemic region and therefore could not have avoided including normally perfused tissue in the so-called "border zone." Domenech<sup>34</sup> carefully outlined the perfusion area of the occluded coronary artery by Evans blue injection and sectioned only the stained areas. He described a threefold radial gradient. But even this is likely to be an overestimate, since total exclusion of normal tissue is probably still not possible. Fischl and colleagues<sup>35</sup> attempted to account for the amount of normally perfused tissue within the perfusion territory of the occluded vessel and observed that if the truly ischemic tissue was analyzed only a negligible gradient existed. Measuring washout of intra myocardial  $Xe^{133}$  depots, Linder<sup>36</sup> also noted a marked decline in blood flow to 10 per cent of normal within a few millimeters of the border between well perfused and ischemic myocardium, and an additional decrease of only 5 per cent to the central zone. Although a definite radial gradient may not be present, blood flow to the ischemic area is probably not homogeneous. Analysis of the three dimensional geometry of ischemic myocardium<sup>37</sup> intravenous fluorescein injection studies<sup>38</sup> and histologic examination<sup>39</sup> of infarcted tissue reveal relatively well perfused normal appearing myocardium amongst necrotic fibers.

If a radial gradient is questioned there is little doubt about a transmural gradient. Endocardial flow is severely depressed while epicardial flow is

4. Hecht H S, Aroesty J M, La Rosa P J, Morkin E and Paulin S. Role of the coronary collateral circulation in the preservation of left ventricular function. *Circulation* 48 (Suppl IV) 87 1973
43. Levin D C and Baltaxe H A. Role of coronary collateral circulation and distal runoff in preserving myocardial contractility. *Circulation* 48 (Suppl IV) 88 1973
44. Levin D C. Pathways and functional significance of the coronary collateral circulation. *Circulation* 50 831 1974
45. Banks V N, Bodenheimer M M and Helfant R H. Determinants of reversible asynergy. Effect of pathologic waves coronary collaterals and anatomic location. *Circulation* 50 714 1974
46. Williams, D O, Amsterdam E A, Müller R R and Mason D T. Functional significance of coronary collateral vessels in patients with acute myocardial infarction. Relation to pump performance, cardiogenic shock and survival. *Am J Cardiol* 37 345 1976
47. Hamby M I, Aintablian A and Schwartz A. Reappraisal of the functional significance of the coronary collateral circulation. *Am J Cardiol* 38 305 1976
48. Webster J E, Moberg C and Runcin G. Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. *Am J Cardiol* 33 180 1974
49. Schaper W. Pathophysiology of coronary circulation. *Prog Cardiovasc Dis* 14 775 1971
50. Lavine P, Filip Z, Najmi, M, Kumbins D, Segal B L and Lihart J W. Clinical and hemodynamic evaluation of coronary collateral vessels in coronary artery disease. *Am Heart J* 87 343 III 4
51. Sullivan J M, Taylor W J, Elliott W C and Gorlin R. Regional myocardial blood flow. *J Clin Invest* 46 1402 1971
52. Smith S C Jr, Gorlin R, Herman M V, Taylor W J and Collins J J Jr. Myocardial blood flow in man. Effects of coronary collateral circulation and coronary artery bypass surgery. *J Clin Invest* 51 7056 1972
53. Goldstein R E, Stinson E B, Scherer J L, Senning R P, Grehl T M and Epstein S E. Intraoperative coronary collateral function in patients with coronary occlusive disease. Nitroglycerin responsiveness and angiographic correlations. *Circulation* 49 298 1974
54. Schaper W. The collateral circulation of the heart. Amsterdam 1971. North Holland Publishing Co.
55. Schaper W, Jageneau A and Khonneux R. The development of collateral circulation in the pig and dog heart. *Cardiologia* 51 371 1967
56. Schaper W, Flameng W and De Bratander M. Comparative aspects of coronary collateral circulation. In Bloor C M editor. *Comparative pathophysiology of circulatory disturbances. Advances in experimental medicine and biology* vol. 9. New York 1972, Plenum Press p 267
57. Wessse A B, Heatney K, Narang H M and Regan T J. Comparison of the coronary collateral circulation in dogs and baboons after coronary occlusion. *Am Heart J* 92 193 III 6
58. Lumb G, Singletary H P and Hardy L B. Collateral circulation following experimental gradual narrowing of the coronary arteries. *Angiology* 13 463 1962
59. Zoll P M and Norman J. The effects of vaso motor drugs and of anemias upon interarterial coronary anastomoses. *Circulation* 6 837 1952
60. Meesmann W, Schulz F W, Schley G and Adolphsen F. Überlebensquote nach akutem experimentellem Koronarschluss in Abhängigkeit von Spontankollateralen des Herzens. *Z Gesamte Exp Med* 163 246 1970
61. Eckstein R W. Coronary interarterial anastomoses in young pigs and mongrel dogs. *Circ Res* 2 460 1954
62. Winbury M M, Losada M, Kessel D, Howe B B, and Pensinger R. II. Pentaerythritol tetranitrate and dipyridamole on cardiac nutritive flow and blood content. *Am J Physiol* 220 1558 1971
63. Marcus M L, Kerber R E, Ehrhardt J and Abboud F M. Three dimensional geometry of acutely ischemic myocardium. *Circulation* 52 204 1975
64. Marcus M L, Kerber R E, Ehrhardt J and Abboud F M. Effects of time on volume and distribution of coronary collateral flow. *Am J Physiol* 230 279 1976
65. Prinzmetal M, Bergman H C, Kruger H E, Schwartz L L, Simkin B and Sobin S S. Studies on the coronary circulation. III. Collateral circulation of beating human and dog hearts with coronary occlusion. *Am Heart J* 35 689 1948
66. Cohn P F, Kirk E S, Downey J M, Sonnenblick E H and Gorlin R. Autoradiographic evaluation of myocardial collateral circulation in the canine heart. *Cardiovasc Res* 7 181 1973
67. Wiggers C J. The problem of functional coronary collaterals. *Exp Med Surg* 8 402, 1950
68. Tennant R and Wiggers C J. The effect of coronary occlusion on myocardial contraction. *Am J Physiol* 132 351 1975
69. Cohen M V, Downey J M, Sonnenblick E H, and Kirk E S. The effects of nitroglycerin on coronary collaterals and myocardial contractility. *J Clin Invest* 52 2836 1973
70. Becker L C, and Pitt B. Collateral blood flow in conscious dogs with chronic coronary artery occlusion. *Am J Physiol* 221 1507 1971
71. Chubukla A A, Lahan B H and Hellema, H A. Myocardial collateral flow measurements in mongrel dogs. *Am J Physiol* 225 559 1973
72. Cohen M V, and Eldh, P. Experimental myocardial infarction in the closed-chest dog. Controlled production of large or small areas of necrosis. *Am Heart J* 86 III 19,3
73. Schaper W, Remijnse P and Khonneux R. The size of myocardial infarction after experimental coronary artery ligation in Kreislaufschon. 58 904 1969
74. Rinaas F, Cobb F R, Bache R J and Greenfield J C Jr. Relationship between blood flow to ischemic regions and extent of myocardial infarction. Serial measurement of blood flow to ischemic regions in dogs. *Circ Res* 38 439 1976
75. Bobb J R, R Kunze D C, McCall W Jr and Green H D. Location of communications between cognate bed of descending ramus of left coronary and adjacent collateral vascular beds. *Proc Soc Exp Biol Med* 69 115 1978
76. Schley G, Meesmann W, Schulz F W and Adolphsen P. Das Flektrokardiogramm nach akutem experimentellem Koronarschluss in Abhängigkeit von Spontankollateralen des Herzens. *Z Kreislaufforsch* 60 405 1971
77. Stephan K, Meesmann W and Sidony V. Oxygen demand and collateral vessels of the heart. Factors influencing the severity of myocardial ischemic injury after experimental coronary artery occlusion. *Cardiovasc Res* 9 640 1976
78. Blumgart H L, Zoll P M, Friedberg, A S and

- 4 Craiciu A. Anatomische Studien über die Coronar arten und experimentelle Untersuchungen über ihre Durchgängigkeit Virchow Arch (Pathol Anat) 228 1 1922
- 5 Campbell J S Stereoscopic radiography of the coronary system Q J Med 22 247, 1929
- 6 Schlesinger M J An injection plus dissection study of coronary artery occlusions and anastomoses AM HEART J 15 528 1938
- 7 Blumgart H L Schlesinger M J and Davis D Studies on the relation of the clinical manifestations of angina pectoris coronary thrombosis and myocardial infarction to the pathologic findings With particular reference to the significance of the collateral circulation AM HEART J 19 1 1940
- 8 Blumgart H L Schlesinger M J and Zoll P M Angina pectoris coronary failure and acute myocardial infarction The role of coronary occlusions and collateral circulation JAMA 116 91 1941
- 9 Zoll P M Wessler S and Blumgart H L Angina pectoris A clinical and pathologic correlation Am J Med 11 331 1951
- 10 Vastesaeger M M van der Straeten P P Friart J Candaele G, Ghys A and Bernard H M Les anastomoses intercoronariennes telles qu'elles apparaissent à la coronarographie post mortem Acta Cardiol 12 365 1957
- 11 Bellman S and Frank H A Intercoronary collaterals in normal hearts J Thorac Surg 36 584 1958
- 12 Fulton W F M Arterial anastomoses in the coronary circulation I Anatomical features in normal and diseased hearts demonstrated by stereoscopy Scot Med J 8 420 1963
- 13 Baroldi G Mantero O and Scamazzoni G The collaterals of the coronary arteries in normal and pathologic hearts Circ Res 4 223 1956
- 14 Baroldi G Functional morphology of the anastomotic circulation in human cardiac pathology Methods Achiev Exp Pathol 5 438 1971
- 15 James T N Anatomy of the coronary arteries in health and disease Circulation 32 1020 1965
- 16 Rodriguez F L and Robbins S L Postmortem angiographic studies on the coronary arterial circulation Intercoronary arterial anastomoses in adult human hearts AM HEART J 70 348 1965
- 17 Gensini C G and da Costa B C B The coronary collateral circulation in living man Am J Cardiol 24 393 1969
- 18 Holyoke J H Coronary arteriosclerosis and myocardial infarction as studied by an injection technique Arch Pathol 39 268 1945
- 19 Zoll P M Wessler S and Schlesinger M J Intercoronary anastomoses in the human heart with particular reference to anemia and relative cardiac anoxia Circulation 4 797 1951
- 20 Zimmerman H A The coronary circulation in patients with severe emphysema cor pulmonale cyanotic congenital heart disease and severe anemia Dis Chest 22 269 1952
- 21 Fulton W F M The time factor in the enlargement of anastomoses in coronary artery disease Scot Med J 11 18 1964
- 22 Jones A M The functional role of intercoronary anastomoses Acta Cardiol (Suppl) 11 130 1965
- 23 Siepser L Kaitman A J Mills N Pughkin T and Fox A C Coronary collateral flow after traumatic fistula between right coronary artery and right atrium N Engl J Med 287 754 1972
- 24 Bourassa M G Lésperance J and David P Conclusions sur le rôle de la circulation collatérale dans la maladie coronarienne Ann Cardiol Angiol 23 4 1974
- 25 Kattus A A Relation of coronary events to spasm of coronary arteries precariousness of obstructive lesions and availability of collateral channels in Bloc C M and Olsson R A editors Current topics in coronary research Advances in experimental medicine and biology vol 39 New York 1973 Plenum Press p 719
- 26 Porter W T An American textbook of physiology Howell W H editor second edition vol 1 Philadelphia 1900 W B Saunders & Company p 180
- 27 Fulton W F M Chronic generalized myocardial ischaemia with advanced coronary artery disease Br Heart J 18 341 1956
- 28 Lesbre J P Calazel P Méné P and Salvador M La circulation coronaire Coeur Med Interne 6 43 1967
- 29 Baroldi G Coronary heart disease Significance of the morphologic lesions AM HEART J 85 1 1953
- 30 Carleton R A and Boyd T Traumatic laceration of the anterior descending coronary artery treated by ligation without myocardial infarction Report of a case with review of the literature AM HEART J 66 136 1958
- 31 Le Capon J Cheiloul N and Roujeau J Les anastomoses inter coronariennes Valeur fonctionnelle et signification pathologique Sem Hop Paris 46 38 1970
- 32 Fulton W F M Anastomotic enlargement and ischaemic myocardial damage Br Heart J 26 1 1964
- 33 Helfant R H Kemp H G and Corlin R Coronary atherosclerosis coronary collaterals and their relation to cardiac function Ann Intern Med 73 189 19 0
- 34 Helfant R H Vokonas P S and Corlin R Functional importance of the human coronary collateral circulation N Engl J Med 284 1277 1971
- 35 Miller R Mason D T Zelis R Bonanno J A and Amsterdam E A Determinants of the coronary collateral circulation in man Development principally related to severity of regional atherosclerosis Clin Res 19 117 1971
- 36 Miller R R Zelis R Mason D T, and Amsterdam E A Relation of coronary collateral vessels to ventricular function in patients with equal extent of coronary artery disease Circulation 44 (Suppl II) 70 19 1
- 37 Mason D T Amsterdam E A Miller R R, Hughes J L III Bonanno J A Iben A B Hurley F J Massumi H A and Zelis R Consideration of the therapeutic roles of pharmacologic agents collateral circulation and saphenous vein bypass in coronary artery disease Am J Cardiol 28 608 1971
- 38 Carroll R J Verani M S and Falsetti H L The effect of collateral circulation on segmental left ventricular contraction Circulation 50 709 1974
- 39 Demany A A Tamba A and Zimmerman H A Correlation between coronary arteriography and the postexercise electrocardiogram Am J Cardiol 19 5 6 1967
- 40 Tuna N and Amplatz K The significance of coronary collateral circulation Coronary arteriographic and electrovectorcardiographic correlations Am J Cardiol 26 663 1970
- 41 Harris C N Kaplan M A, Parker D I Aronow W S and Fliedstad M H Anatomic and functional correlates of intercoronary collateral vessels Am J Cardiol 30 611 1972

### Fibrin deposition on a pacemaker catheter in a heparinized patient

Transvenous right ventricular cardiac pacing for disorders of cardiac rhythm has been a recognized clinical tool for a number of years. Reports of thrombotic complications involving temporary transvenous pacing catheters are rare.

Recently a 30-year-old man was admitted to our coronary care unit with an inferior myocardial infarction. On the first hospital day 7,500 units of heparin was begun and continued every four hours sufficient to produce slightly prolonged partial thromboplastin times 3.5 hours after each dose. During the second hospital day progressive AV block necessitated the placement of a temporary transvenous right ventricular pacemaker. A Cordis bipolar percutaneous electrode (Catalog number 3,0-110) was positioned in the right ventricle via a left median antecubital venous cut-down. The pacemaker functioned well for eleven days with only minimal increase in milliamperage. When the pacemaker was removed a thin layer of tissue 1 to 2 mm in thickness was observed tightly adherent to the catheter and partially encircling it. It began 6 cm from the catheter tip and extended proximally 6 cm. Pathologic examination of the thrombus revealed it to be 1 to 2 mm in thickness with the greatest density in the proximal portion. It was friable and had a laminated appearance. Microscopically there were strips of fibrin alternating with

layers of cells mainly neutrophils. The area directly adherent to the catheter was acellular. In several areas on the external surface of the thrombus flattened endothelial like cells were seen (Fig 1). Trichrome stain revealed no evidence of collagen.

Surface thrombus deposition on intravascular devices has been reported involving Swan-Ganz Catheters, central venous pressure catheters, and transvenous pacemakers. Goldberg described a single patient with a right ventricular thrombus at the catheter pole in a series of 115 patients transvenously paced in excess of one week on no anticoagulant. He concluded that no aggregates of blood elements greater than waxy fibrin clots have been found on any catheter. Forrester and associates reported that Swan-Ganz Catheters left in position up to 96 hours in 40 critically ill patients revealed no evidence of thrombus formation. Gott reports that heparin over a wide concentration range will not only inhibit the generation of thrombin in plasma but block the action of fibrin on fibrinogen and block platelet agglutination by formed thrombin on transvenous catheters. Our patient was well heparinized and yet significant thrombus deposition occurred. The position of the thrombus formation suggests formation in the right atrium similar to the pathologic findings of Becker and co-workers. Thus heparin in full

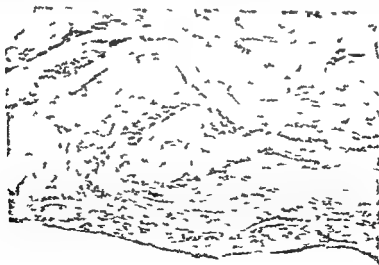


Fig 1 Thrombotic material stripped from catheter demonstrating laminated appearance (Hematoxylin and eosin original magnification  $\times 250$ )



- Gilgus D R The experimental production of inter coronary arterial anastomoses and their functional significance *Circulation* 1 10 1950
- 79 Garza D A, White F C Hall R E and Bloor C M Effect of coronary collateral development on ventricular fibrillation threshold *Basic Res Cardiol* 69 371 1974
- 80 Cohen M V Holman B L and Kirk E S Coronary collaterals Determinant of infarct size *Clin Res* 22 678A 1974
- 81 Bishop S P White F C and Bloor C M Regional myocardial blood flow during acute myocardial infarction in the conscious dog *Circ Res* 38 429 1976
- 82 Elliot E C Hemodynamic evidence of the development of coronary collateral circulation in conscious dogs in Bloor C M and Olsson R A editors Current topics in coronary research Advances in experimental medicine and biology vol 39 New York 1973 Plenum Press p 173
- 83 Pasyk E Bloor C M Khouri E M and Gregg D E Systemic and coronary effects of coronary artery occlusion in the unanesthetized dog *Am J Physiol* 220 646 1971
- 84 Elliot E C Khouri E M Snow J A and Gregg D E Direct measurement of coronary collateral blood flow in conscious dogs by an electromagnetic flow meter *Circ Res* 34 374 1974
- 85 Smith H J, Singh B N Norris R M John M B, and Hurley P J Changes in myocardial blood flow and ST segment elevation following coronary artery occlusion in dogs *Circ Res* 36 697 1975
- 86 Schaper W and Pasyk S Influence of collateral flow on the ischemic tolerance of the heart following acute and subacute coronary occlusion *Circulation* 53 (Suppl 1) 57 1976
- 87 Huzel H O Nelson G R Sonnenblick E H and Kirk E S Redistribution of collateral blood flow from necrotic to surviving myocardium following coronary occlusion in the dog *Circ Res* 39 214 1976
- 88 Becker L C, Ferreira R and Thomas M Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion *Cardiovasc Res* 7 391 1973
- 89 Domenech R J Total and regional coronary blood flow during acute coronary occlusion in anesthetized and conscious dogs *Cardiovasc Res* 8 415 1974
- 90 Fischl S J Sonnenblick E H and Kirk E S Collateral blood flow in the border zone following acute coronary occlusion *Am J Cardiol* 35 136 1975
- 91 Linder E Measurements of normal and collateral coronary blood flow by close arterial and intramyocardial injection of Krypton and Xenon *Acta Physiol Scand* 68 (Suppl 272) 5 1966
- 92 Kloner R A Ganote C E and Jennings R B The no reflow phenomenon after temporary coronary occlusion in the dog *J Clin Invest* 54 1496 1974
- 93 Meneely G R The capillary factor in myocardial infarction *Am J Cardiol* 34 581 1974
- 94 Trump B F Discussion Effects of hyperosmotic mannitol in reducing ischemic cell swelling and minimizing myocardial necrosis *Circulation* 53 (Suppl 1) 52 1976
- 95 Willerson J T Powell W J Jr Gurney T E Stark J J Sanders C A and Leaf A Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol *J Clin Invest* 51 2989 1972
- 96 Willerson J T Watson J T, Hutton I, Fixler D E, Curry G C and Templeton G H The influence of hypertonic mannitol on regional myocardial blood flow during acute and chronic myocardial ischemia in anesthetized and awake intact dogs *J Clin Invest* 55 89 1975
- 97 Smith E R Redwood D R McCarron W F and Epstein S E Coronary artery occlusion in the conscious dog Effects of alterations in arterial pressure produced by nitroglycerin hemorrhage and alpha adrenergic agonists on the degree of myocardial ischemia *Circulation* 47 51 1973
- 98 Watson J T Willerson J T Fixler D E Browning R M and Sugg W L Changes in collateral coronary blood flow distal to a coronary occlusion during intra aortic balloon pumping *Trans Am Soc Artif Intern Organs* 19 402 1973
- 99 Jacobey J A Taylor W J Smith G T Gorha R and Harken D E A new therapeutic approach to acute coronary occlusion II Opening dormant coronary collateral channels by counterpulsation *Am J Cardiol* 11 218 1963
- 100 Watson J T Fixler D E Platt M R Nall B B, Jett G K and Willerson J T The influence of combined intra aortic balloon counterpulsation and hyperosmotic mannitol on regional myocardial blood flow in ischemic myocardium in the dog *Circ Res* 38 506 1976
- 101 Cohen M V Sonnenblick E H and Kirk E S Coronary steal Its role in the detrimental effect of isoproterenol after acute coronary occlusion in dogs *Am J Cardiol* 38 880 1976
- 102 Cohen M V Sonnenblick E H and Kirk E S Comparative effects of nitroglycerin and isosorbide dinitrate on coronary collateral vessels and ischemic myocardium in dogs *Am J Cardiol* 37 244 1976
- 103 Eckstein R W Effect of exercise and coronary artery narrowing on coronary collateral circulation *Circ Res* 5 230 1957

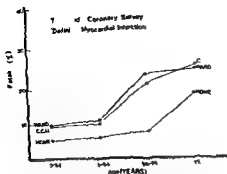


Fig 1 Graphic and tabular presentation of deaths from myocardial infarction in the Tees-side survey. A comparison is made of deaths occurring at home, in the hospital ward and in the coronary care unit.

FATALITY BY AGE AND PLACE OF TREATMENT

| AGE   | HOME |        |      | WARD |        |      | CCU  |        |      |
|-------|------|--------|------|------|--------|------|------|--------|------|
|       | nos. | deaths | %    | nos. | deaths | %    | nos. | deaths | %    |
| 5-64  | 37   | 2      | 5.4  | 52   | 5      | 9.6  | 62   | 8      | 12.9 |
| 65-74 | 63   | 3      | 4.7  | 81   | 10     | 12.3 | 98   | 10     | 10.2 |
| 75-84 | 71   | 6      | 8.4  | 102  | 25     | 24.5 | 7    | 10     | 21.3 |
| 85+   | 37   | 6      | 16.2 | 81   | 21     | 25.9 | 11   | 3      | 27.3 |

urban population (396 000) in the north-east of England. Published results from the survey include details about incidence, mortality and fatality of attacks—the schedule of events leading to patients coming under care, the frequency and relevance of premonitory symptoms and the fatality rates of patients treated at home and in hospital. It is this last aspect that is particularly considered in this annotation. I am obliged to my co-authors for their permission to reproduce some of our results.

A total of 2 171 attacks were reported usually by family doctors, with a positive diagnosis of either "definite" or possible myocardial infarction in 1 938 cases. Of these 99 patients died within 98 days of onset of the attack, giving an episode fatality rate of 60.5 per cent.

During the first 6 months of the survey, 476 patients died and a detailed scrutiny was carried out of the circumstances of their death. This revealed that for 65 per cent of this group there was either no interval between onset of attack and death or the interval was unknown, almost all because the death was witnessed.

Eighteen per cent of the deaths occurred between onset of attack and 19 hours later. It is this rather small group of 19 cases for whom emergency services like mobile units would be most effective. A further 17 per cent died between 19 hours and 98 days after onset of attack.

Cases were classified as treated in this survey only if data (history, physical examination, ECG, cardiac enzymes) for diagnostic assessment had been collected. Quite fortuitously patients fell almost equally into three treatment groups. Of the 1 109 patients, 374 were treated at home, 397 were in hospital wards and 334 were in coronary care units. (Fourteen patients were excluded because insufficient data were available but none of these patients died.)

The restriction of the analysis to assessed cases gave rise to two problems. First, the interval from onset to assessment was different for different treatment groups. Hospital cases were seen fairly consistently between 3 and 4 hours after the attack, but the interval for home patients varied from 11 to 12 hours, according to whether the case was notified during the day or night. Second, of the 64 patients who died between onset and assessment, 63 had been referred to hospital. If cases had been admitted to the analysis at the point at which place of treatment had been chosen rather than at the point of diagnostic assessment, hospital fatality rates would have appeared much worse.

Table 1 Age standardized fatality rates (in per cent) in patients with definite myocardial infarctions by place of treatment

|       | Home | Ward | Coronary Care Unit (CCU) |
|-------|------|------|--------------------------|
| Men   | 7.3  | 14.8 | 14.8                     |
| Women | 9.0  | 16.9 | 17.6                     |

There was no difference between the three groups in terms of shock, history, rhythm changes and ECG abnormalities. The Peel Index, modified to incorporate additional data in this survey, was used to assess severity and showed no difference between patients treated in home ward or CCU. But there were differences for age (Fig 1) and serum aspartate aminotransferase (SGOT) levels. Accordingly, the fatality rates given in Table 1 have been standardized for age. Further standardization for SGOT levels do not alter the figures appreciably.

One major difference between home and hospital treated patients was revealed in the timing of events prior to the patients coming on to treatment. In the case of hospital treated patients, the call was made to the doctor half an hour earlier than for home treated patients (median times from onset 1 hour and 1½ hours). In addition, the doctor reached the patient twice as quickly (median times half an hour and 1 hour). These differences were not related to the mode of onset—sudden or gradual—or to whether the main symptom was pain, syncope, dyspnoea or dysrhythmia.

One way of explaining these results would be in terms of the way in which the patient and his family react to the crisis. If the family physician is faced with a home situation which conveys panic and alarm, he will seek to act decisively and would therefore probably opt for hospital treatment. It is this very feeling that decisive action necessarily means hospital that this and other studies have brought into question.

R J Donaldson MB DPH FFCM

London School of Hygiene and

Tropical Medicine

Keppel Street

London WC1E 7HT

England

therapeutic doses does not provide absolute protection against thrombus formation on indwelling cardiac catheters. In a patient with acute myocardial infarction, thrombus formation may occur and could act as a source of pulmonary embolic disease despite adequate heparin therapy.

Robert M MacMillan MD Major USAF MC  
Division of Cardiology  
Malcolm Grou USAF Medical Center  
Andrews Air Force Base  
Washington D C  
Randall W Strafe MD Major USAF MC  
Armed Forces Institute of Pathology  
Washington D C

#### REFERENCES

- 1 Goldberg E Complications of pacemaker therapy for heart block *Am J Cardiol* 17:439 1966
- 2 Zucker I R Parsonnet V Gilbert L and Asa M Dipolar electrode in complete heart block, *JAMA* 184:549 1963

- 3 Swan H J C Ganz W Forrester J Marcus H Diamond G and Chonette D Catheterization of the heart in man with the use of a flow directed balloon tipped catheter *N Engl J Med* 283:447 1970
- 4 Henzel J H and DeWeese M S Morbid and mortal complications associated with prolonged central venous cannulations *Am J Surg* 121:600 1971
- 5 Becker A M Becker M J Martin F H, and Edwards J E Bland thrombosis and infection in relation to intracardiac catheter *Circulation* 46:900 1972
- 6 Becker A E Becker M J Claudon M D and Edwards J E Surface thrombosis and fibrous encapsulation of intravenous pacemaker catheter electrode *Circulation* 46:409 1972
- 7 Forrester J S Ganz W Diamond G McHugh T Chonette D W, and Swan H J C Thermomodulation cardiac output determination with a single flow directed catheter *AM HEART J* 83:306 1972
- 8 Gott V L The causes and prevention of thrombosis on prosthetic materials *J Surg Res* 6:214 1968

## Of diastolic and systolic pressure and left ventricular work

The usual opinion in clinical medicine is that the level of the diastolic pressure is more important than the level of systolic pressure and that the higher the diastolic pressure (DP) the greater the work of the left ventricle (LV). There is a tendency to ignore the systolic blood pressure (SP) and the pulse pressure (PP) is rarely ever even mentioned. But when the aortic valve is functioning normally the diastolic pressure in the aorta and arterial system does not impose its load upon the LV. This pressure is supported by the aortic valve cusps during ventricular diastole when the cavity of the left ventricle is isolated from the arterial system and its intraluminal pressure. However as the LV contracts and raises intraventricular pressure to a level that just exceeds the pressure in the aorta the aortic cusps open and the cavity of the LV and the arterial system become continuous. The ventricle continues to contract to reach its maximal pressure level which is systolic pressure. The systolic pressure and the time course of pulse pressure then determine the level of the maximal pressure load imposed upon the LV. The length of time that the aortic cusps are opened determines the duration during which pulse pressure and systolic pressure are imposed

upon the LV wall. The integral of the time course relation of the intracavitary pressure of the left ventricle to left ventricular volume during a cardiac cycle reflects the time course of work of the left ventricle per heart beat. Thus as indicated a number of years ago the time course of the pressure-volume relationship of the left ventricular cavity defines the time course of LV work and also determines the time course of tension of the left ventricular wall. However the systolic pressure as well as diastolic pressure determines the time course of work and tension. The systolic pressure and time course of pulse pressure must receive serious consideration in cardiology.

C E Burch MD  
Tulane University School of Medicine  
and Charity Hospital of Louisiana  
New Orleans La

#### REFERENCE

- 1 Burch G M Ray C T and Cronvich J A Certain mechanical peculiarities of the human cardiac pump in normal and diseased states *Circulation* 5:504 1971

## At home or to hospital?

The possibility that an acute serious illness might be better treated at home would seem to be contrary to orthodox medical thinking. Yet there are pointers and they are more than just straws in the wind to suggest that in the case of

acute myocardial infarction many of the sufferers would be better off treated in the familiarity of their own home.

One such pointer comes from a survey of attacks of acute myocardial infarction occurring in a 12 month period in an

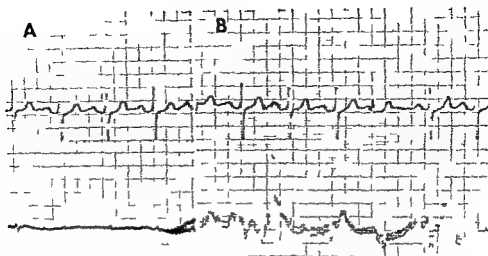


Fig 2 Dynamic electrocardiogram of patient 2. Channel one above channel two below A During waking hours B While under the electric blanket

sleep under an electric blanket during the time of continuous 24 hour electrocardiography to avoid this interference

Joseph A Gascho MD

Maury C Newton Jr MD

University of Virginia School of Medicine

Division of Cardiology

Charlottesville VA 22901

Present addresses

Joseph A Gascho MD

University of Iowa Hospitals and Clinics

Division of Cardiology

Iowa City IA 52241

Maury C Newton Jr MD

787 Campbell Hill Street

Marietta GA 30064

#### REFERENCE

- 1 Krasnow A Z and Bloomfield D K Artifacts in portable electrocardiographic monitoring. *Am Heart J* 91:349 1976

# REFERENCES

- 1 Mather H G Pearson N G Read K L et al Acute myocardial infarction home and hospital treatment *Br Med J* 3 334 1971
- 2 Colling A Dellipiani A W Donaldson R J and McCormack P Teesside coronary survey an epidemiological study of acute attacks of myocardial infarction *Br Med J* 2 1169 1976
- 3 World Health Organization Hypertension and coronary heart disease Technical Report Series No 168 Geneva 1969 WHO
- 4 Peel A A F Semple T Wang I Lancaster W M and Dill J L A coronary prognostic index for grade 1 the severity of infarction *Br Heart J* 24 46 1962

## Electromagnetic interference in dynamic electrocardiography caused by an electric blanket

Although numerous causes of artifacts in dynamic electrocardiography have been noted we are unaware of reports of electromagnetic interference as a cause of artifact. A recently observed example of this type of interference is described here.

A 49 year old white female with a diagnosis of idiopathic ventricular tachycardia had 24 hour dynamic electrocardiography with an Avionics Model No 425 electrocardiograph. An Avionics Dynamic Electrocardioscanner 660 was used in analysis of the 24 hour tape. During the sleeping hours there was marked 60 Hz interference that made both channels of the printout uninterpretable (Fig 1). During a 30 minute period when the patient arose from sleep this interference completely cleared. We looked for possible causes of this electromagnetic interference and found the patient had slept

under an electric blanket. To see if the electric blanket was the cause of the interference two other Holtered subjects slept under an electric blanket. As noted in Fig 2, one channel of the ambulatory electrocardiogram showed marked electrical interference during this time. Patient 3 (not illustrated) also slept under an electric blanket and although the electrocardiogram was easily interpretable 60 Hz interference was noted on one channel at periodic times during the night. In all three of these patients dynamic electrocardiograms during the remainder of the time were technically adequate tracings.

Our conclusion is that electric blankets can interfere with the electrocardiogram recorded during dynamic monitoring. This interference may render a considerable portion of the monitoring uninterpretable and therefore decrease efficacy of Holter monitoring. We would recommend that patients not

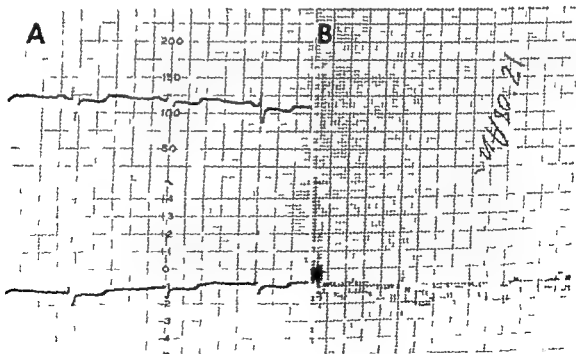


Fig 1 Dynamic electrocardiogram of patient 1. Channel one above. Channel two below. A During waking hours. B While under the electric blanket.

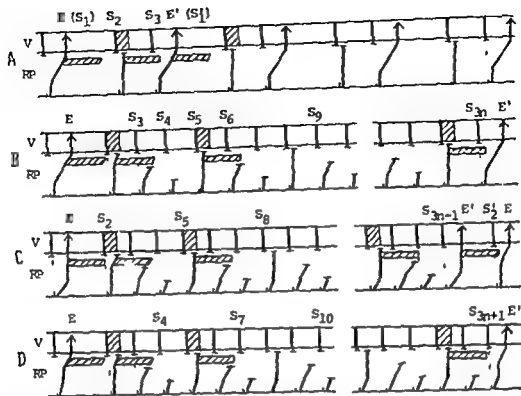


Fig 1 Strips illustrating a manifest trigeminy (strip A) and a classical form (strip B) and two variants (strips C and D) of concealed trigeminy. Shaded areas represent the refractory period. Intraventricular conduction of the sinus impulse leading to the re-entry path is indicated by dashed lines. Conduction in the re-entry path for the extrasystolic impulse re-entering into the path is not indicated here because the conduction appears to be blocked at a proximal site of the re-entry path and bring about no significant effect on the next sinus impulse conducted into the path. E = extrasystole S and (S) = sinus impulses conducted and non conducted to the ventricles respectively V = ventricles RP = re-entry path

- Katou K Oda M Yamamoto K, Kamada H and Yoshida T Impulse conductivity in the region surrounding the extrasystolic focus Wenckebach phenomenon of the coupling interval and the rule of multiples. *Saishin Igaku* 15 1865 1960 (in Japanese)
3. Schamroth L, and Marmot H J L. Concealed ventricular extrasystoles. *Circulation* 27 1043 1963
  4. Kinoshita S. Concealed ventricular extrasystoles due to interference and due to exit block. *Circulation* 52 230 1955
  5. Kinoshita S and Tanabe Y. Variants of concealed bigeminy. *Circulation* 52 966 1975
  - Kosowsky B D, Latif P and Radoff A M. Multilevel antenodal block. *Circulation* 54 914 1956
  - Lightfoot P R. Concealed extrasystolic ventricular bigeminy with interpolation. *Chest* 67 3 3 1975

certain regular patterns, critical analysis of such patterns may provide some insight into the underlying electrophysiological mechanisms

The mechanisms we have proposed in a recent issue of this journal to account for classical concealed trigeminy and two of its variants are consonant with known electrophysiological phenomena. The mechanisms proposed by Dr Kinoshita are also feasible. It is certainly not possible to choose between the two alternatives with certainty nor to rule out still other reasonable possibilities.

Our preference for the hypothesis outlined in our paper was guided in part by the fact that the extrasystoles were late and many fusion beats were seen. This is clearly illustrated in our Fig 5 which depicts our concept of the mechanism for the classical form of concealed trigeminy. Extrasystole II follows two conducted sinus beats ( $S = 2$ ) and it begins near the peak of a P wave. It is followed by five more conducted sinus beats ( $S = 5$ ). Had the conduction time around the reentry loop after sinus beat R been slightly greater an extrasystole would not have been manifest after R. The reentrant impulse would have been concealed by virtue of "interference." Consequently there would have been eight conducted sinus beats ( $S = 8$ ) in the interectopic interval between R and R.  $S = 2$ , 5 and 8 conducted sinus beats are all compatible with the

## Reply

### To the Editor

In patients with frequent extrasystoles, it is not possible at present to record the electrical activity directly from the ectopic focus or reentry loop. When the extrasystoles occur in

## Mechanism of concealed trigeminy

To the Editor

I have read with great interest the report by Dr Levy and colleagues on two variants of concealed trigeminy. In 1960<sup>1</sup> before Schamroth and Marnott, we reported a case showing the phenomenon of classical concealed trigeminy namely that sinus impulses intervening between two successive ventricular extrasystoles were generally in multiples of three ( $3n$  where  $n$  is any positive integer). The sinus impulses here include those both conducted and nonconducted to the ventricles. Before seeing the cases of Dr Levy and colleagues<sup>1</sup> we had also believed their assumption namely that in all cases of classical concealed trigeminy a 3:1 exit block occurs at the same site in the re-entry path indicating that the refractory period of this site is longer than twice the sinus cycle though it is shorter than three times the sinus cycle. At the present time however I think that some cases of classical concealed trigeminy may be governed by another mechanism. In this letter I would like to offer possible explanations for the cases of Dr Levy and colleagues which are different from those postulated by them.

It seems to me that their cases of concealed trigeminy are a variant of 3:2 Wenckebach exit block due to concealed conduction into the re-entry path. The mechanism is illustrated by diagrams in Fig 1. The longest refractory period in the re-entry path here is shorter than twice the sinus cycle. The refractory period is represented by shaded areas.

Strip A shows a (manifest) trigeminal rhythm which occurs in a comparatively slow sinus rhythm. The first sinus impulse ( $S_1$ ) following the manifest extrasystole  $E$  is blocked at the atrioventricular (A-V) junction. Thereafter the sinus impulse  $S_2$  conducted to the ventricles falls long after the refractory period of the re-entry path. As a result it reaches the distal end of the path without enough delay and becomes a concealed extrasystole due to interference. On the other hand the next conducted sinus impulse  $S_3$  falls shortly after the refractory period of the re-entry path so that it reaches the distal end of the path after marked delay and becomes a manifest extrasystole  $E$ . The sinus impulse ( $S_4$ ) subsequent to the extrasystole  $E$  is again blocked in the A-V junction. This phenomenon is similar to 3:2 Wenckebach exit block though a block recovering conduction of the next sinus impulse occurs in the A-V junction. The presence of such a trigeminal rhythm was indicated in my previously reported patients with a variant of concealed bigeminy.

Strip B shows a classical concealed trigeminy caused by a variant of 3:2 Wenckebach exit block. The sinus rate is somewhat rapid as compared with that in strip A. Therefore the sinus impulse  $S_2$  subsequent to a concealed extrasystole due to interference is blocked at some site in the re-entry path (site A) after it invades markedly slowly a considerably large part of the path. In other words it becomes a concealed extrasystole due to exit block. As a result the next sinus impulse  $S_3$  is blocked at another site in the path (site B) which is proximal to site A. Namely block (not interference) of the sinus impulses here occurs at two different sites in the

re-entry path. After a block at the proximal site B the sinus impulse  $S_5$  again passes through the re-entry path without enough delay and becomes a concealed extrasystole due to interference. In the A-V junction such a variant of 3:2 Wenckebach block due to concealed A-V conduction has been indicated for example in patient 27 displaying 3:1 A-V block that is recently reported by Kosowsky and associates (their Fig. 7).<sup>2</sup>

The terminal part of strip B shows that when the sinus cycle somewhat lengthens a sinus impulse follows a concealed extrasystole due to interference i.e. the impulse  $S_5$  falls shortly after the refractory period of the path and again becomes a manifest extrasystole  $E$ . Thus the number of the interectopic sinus impulses becomes a multiple of three.

In Case 1 of Dr Levy and colleagues too such long sinus cycles favored the appearance of extrasystoles during classical concealed trigeminy. The same feature has been disclosed in some variants of concealed bigeminy.<sup>1</sup> In Cases 2 and 3 of Dr Levy and colleagues bigeminal rhythm occasionally occurred. These findings strongly suggest that the refractory period of the re-entry path in their cases is shorter than twice the sinus cycle.

Strips C and D illustrate two variants of concealed trigeminy in which the sinus rate is more rapid than that in strip B though the refractory period of the re-entry path remains shorter than twice the sinus cycle. As a result of such a rapid sinus rate conduction in the re-entry path is considerably delayed even in the region proximal to site B. Thus when in strip C showing one of the variants the sinus rate is increased beyond a certain critical value (CR) the sinus impulse  $S_{2n+1}$  gives rise to a manifest extrasystole  $E$  despite the fact that this impulse falls long after the refractory period of the distal site (site A). On the other hand when in strip D illustrating the other variant the sinus rate is increased beyond another critical value (CR) the sinus impulse  $S$  following a concealed extrasystole due to interference is blocked at the proximal site (site B) before occurrence of the variant shown by strip C. As a result the next sinus impulse  $S_{2n+1}$  falls comparatively shortly after the refractory period of site A resulting in a manifest extrasystole  $F$ . In cases in which CR is lower than CR<sub>1</sub> the variant illustrated by strip C occurs in which the numbers of interectopic sinus impulses are multiples of three minus 1 ( $3n - 1$ ) indicating Cases 2 and 3 of Dr Levy and colleagues. Conversely in cases in which CR is lower than CR<sub>2</sub> the variant illustrated by strip D occurs in which the numbers of interectopic sinus impulses are multiples of three plus 1 ( $3n + 1$ ) indicating their Case 1.

Shunji Kurohita M.D.

Second Department of Medicine  
Hokkaido University School of Medicine  
Sapporo Japan

## REFERENCES

- 1 Levy M N, Moss L, and Heron N. Two variants of concealed trigeminy. *AM HEART J* 93:183, 1977.
- 2 Satou T, Kurohita S, Tanabe Y, Kawasaki T.

## Reply

## To the Editor

We thank Dr Puech for calling our attention to his previously reported excellent work concerning recording of left atrial activity from the pulmonary artery. It appears that we have rediscovered that which is already known. We therefore give priority to Dr Puech for his original observations. We are pleased to be able to confirm his previous work.

Fernando Amat y Leon M.D.  
Assistant Professor of Medicine  
Cardiology Section

Kenneth M. Rosen M.D.  
Professor of Medicine  
Chief, Cardiology Section

Department of Medicine  
Abraham Lincoln School of Medicine  
University of Illinois College of Medicine  
P.O. Box 6898 Chicago, Ill. 60680

## Preceptorships at major medical centers

## To the Editor

I want to endorse the recommendation of Dr Myron H. Schoenfeld in the *AMERICAN HEART JOURNAL* of May 1977 page 66. I would agree that the only satisfactory solution for the physician surgeon to learn new techniques is to have practical experience at a major medical center and it would seem a short Preceptorship would be an excellent method.

Philip H. Livingston M.D.  
111 Prout Street Building  
Chattanooga Tenn 37402

## Sudden deaths from IHD by age and sex

## To the Editor

Several studies have reported that the percentage of sudden deaths is higher for younger men than for older men. This has also been contradicted. I have recently studied all 12 deaths from ischemic heart disease (International Classification of Diseases 8th ed., No 410-414) in Vermont. This was a year in which there were very few deaths from influenza. All coding was done by the same person at the Vermont State Health Department. When there was more than one cause of death listed on the certificate the underlying cause as determined by a physician was coded.

Each death certificate was individually read and information was recorded on age, sex, and interval between onset of terminal episode and death. Criteria similar to those suggested by Gillum and associates were used to determine eligibility. There were 1464 deaths in the 410-414 category but for various reasons such as death caused by stroke death in surgery death caused by sepsis, etc. 30 cases were rejected making the number studied 1434. Of these 1434 cases interval information was available on 814 per cent or 151 cases.

I have found that younger males and females have a higher

Table 1 Per cent sudden deaths (up to 1 hour) from IHD by age and sex Vermont 1972

|        | Age (years) |       |       |       |       |         |
|--------|-------------|-------|-------|-------|-------|---------|
|        | 30-45       | 46-55 | 56-65 | 66-75 | 76-85 | Over 85 |
| Male   | 40          | 72    | 56    | 45    | 49    | 29      |
| Female | 32          | 74    | 54    | 47    | 33    | 21      |

percentage of sudden deaths than older males and females.

Inherent here is the problem of correctness of the death certificates. Gillum and colleagues found in 56 cases of IHD deaths in Framingham that death certificates were correct 70 per cent of the time in determination of sudden death using 1 hour as a definition of sudden death. Thus it is probable that the data presented here may not be totally correct but nevertheless the over all trend is impressive.

Recently a historical prospective study on the relationship between ventricular premature contractions on routine ECG and subsequent death from coronary heart disease was performed on North Carolina factory workers. The authors used death certificates as the sole source of information to establish cause of death and to divide the interval between onset of symptoms and death into 1 hour sudden deaths, 24 hour sudden deaths, and non sudden deaths.

Since deaths in younger persons are the most premature and therefore the most important to prevent it would seem worthwhile to study this situation further. Thank you.

Richard W. Hodess B.A.  
Dept. of Geography  
University of Alaska Fairbanks  
Fairbanks, Alaska 99701

## REFERENCES

1. Yater W, M. Welsh F, P. Stapleton J, F., et al. Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups. A study of 950 autopsied cases from the Armed Forces Institute of Pathology. *Ann Intern Med* 34:352, 1951.
2. Zukel W, J. Cohen B, M. Mattingly T, W., et al. Survival following first diagnosis of coronary heart disease. *Am Heart J* 78:159, 1969.
3. McNeill R, H. and Pemberton J. Duration of last attack in 998 fatal cases of coronary artery disease and its relation to possible cardiac resuscitation. *Br Med J* 3:139, 1968.
4. Kuller L. and Lillienfeld, A. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. *Circulation* 34:1056, 1966.
5. Margolis J, Gillum R, F. Feinleib M., et al. Community surveillance for coronary heart disease. The Framingham Cardiovascular Disease Survey—Comparisons with the Framingham Heart Study and previous short term studies. *Am J Cardiol* 37:61, 1976.
6. Gillum, R. F. Feinleib M. and Margolis J. R. Community surveillance for cardiovascular disease. The Framingham Cardiovascular Disease Survey. *J Chronic Dis* 29:289, 1976.
7. Fisher F. D. and Tyrer H. A. Relationship between ventricular premature contractions on routine electrocardiography and subsequent death from coronary heart disease. *Circulation* 47:812, 1973.



existence of classical concealed trigeminy ( $S = 3n - 1$  where  $n$  is any positive integer)

The mechanism proposed by Dr Kinoshita involves critical changes in the sinus cycle length. In our Fig 1 the sinus cycle lengths immediately after each of the two extrasystoles in the top strip are less than the sinus cycle length after the first extrasystole in the second strip. This longer cycle in the second strip is followed by another extrasystole after only two conducted sinus beats ( $S = 2$ ). In the top strip however  $S = 5$  after each of the extrasystoles. The shorter sinus cycle lengths immediately after the extrasystoles in the top strip are consonant with Dr Kinoshita's hypothesis for a manifest extrasystole did not appear after these short cycles i.e., after the second sinus R wave. Presumably the extrasystoles after the second sinus R waves in both interectopic intervals in the top strip were concealed. However the sinus R-R intervals that followed immediately after the second extrasystole in the second strip ( $S = 5$ ) and after the first extrasystole in the third strip ( $S = 11$ ) were not detectably shorter than the first sinus R-R interval in the second strip ( $S = 2$ ). On the basis of Dr Kinoshita's theory one might therefore have expected manifest extrasystoles after the second sinus R wave that followed the second extrasystole in strip 2 (instead of after the fifth R wave) and after the second sinus R wave that followed the only extrasystole in strip 3 (instead of after the eleventh R wave).

Precise measurements of electrocardiograms from a larger series of patients will undoubtedly provide a more secure basis for unraveling the mechanism responsible for these fascinating arrhythmias. Rational hypotheses such as those proffered by Dr Kinoshita provide the cardiologist with a logical framework with which to guide such critical measurements. Such analyses will lead to modifications of the existing hypotheses and successive modifications should more closely approximate the truth.

Matthieu N Levy MD  
Division of Investigative Medicine  
M1 Sinai Hospital  
1800 E 105th Street  
Cleveland Ohio 44106

#### REFERENCE

- 1 Levy M N, Mon I and Kenn N. Two variants of concealed trigeminy. *Am Heart J* 93:183-188, 1977.

#### Indirect recording of left atrial activation in the main pulmonary trunk

To the Editor

In the March 1977 issue of this JOURNAL, Amat y Leon and colleagues give a beautiful example of left atrial recording by positioning an electrode catheter in the main pulmonary trunk. We share their opinion on the interest of this supplementary way of exploring left atrial activity more precisely than that of the left atrial appendage when the tip of the electrode catheter is close to the left border of the pulmonary artery.

We used this new approach more than 20 years ago many

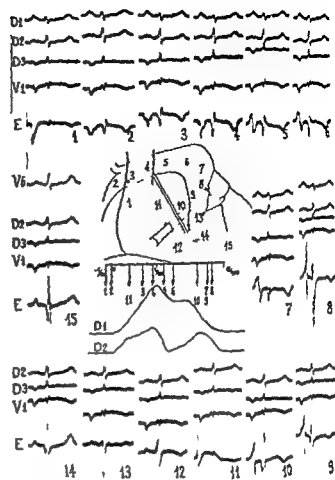


Fig 1 Intracavitary mapping of the atrial activation in a case of left atrial enlargement (mitral stenosis)

examples of atrial mapping including atrial electrograms recorded in the pulmonary artery were obtained in normal and pathological cases and were illustrated in the old books dedicated to intracardiac electrocardiography. Fig 1 is a representative example of atrial mapping performed with unipolar electrodes. The modern use of bipolar electrograms for timing atrial depolarization is undoubtedly more accurate.

We congratulate Dr Rosen's group for informing the English speaking readers about this third alternative to the indirect exploration of the left atrium in addition to esophageal and coronary sinus leads which must be considered for clinical applications in cases of ectopic atrial activation.

J Puech MD  
Professor of Experimental Cardiology and  
Vascular Disease  
Faculty of Medicine  
31000 Montpellier, France

#### REFERENCES

- 1 Amat y Leon F, Deedwania P, Miller R H, Bhargava R C and Rosen R M. A new approach for indirect recording of anterior left atrial activation in man. *Am Heart J* 93:408-1977.
- 2 Puech P. L'activité électrique auriculaire normale et pathologique vol 1 Paris 1967 Masson & Co.
- 3 Latour H, and Puech P. L'Electrocardiographie endocavitaires vol 1 Paris 1967 Masson & Co.

## Books received

---

Quality Control in Nuclear Medicine Radiopharmaceuticals Instrumentation and In Vitro Assays Edited by Buck A Rhodes St Louis 1977 The C V Mosby Company 455 pages Price \$39.50

Local Anesthetics 2nd edition By Rudolph H de Jong M D Springfield Ill 1977 Charles C Thomas Publisher 275 pages Price \$32.50

Pathophysiology and Therapeutics of Myocardial Ischemia Edited by Allan M Lefer Gerald J Hellmer and Michael J

Rovetto Jamaica N Y, 1977 Spectrum Publications, Inc., 530 pages Price \$38.50

✓ The Prostaglandins vol 3 Edited by Peter W Ramwell New York 1977 Plenum Publishing Corp 347 pages Price \$39.50

Guide to Fitness after 50 Edited by Raymond Harris M D., and Lawrence J Frankel, New York, 1977 Plenum Publishing Corp 338 pages Price \$24.50

## Book reviews

**Rheology of Blood in Diagnostic and Preventive Medicine** By Leopold Dintenfass London 1976 Butterworth & Co Ltd 396 pages Price \$27.95

Physicians including cardiologists and vascular physicians and surgeons give relatively little consideration to rheology of blood. They fail to even realize the importance of blood viscosity in peripheral blood flow. The hydraulic and hemodynamic aspects of the circulation must be borne in mind constantly when treating patients with cardiovascular disease. This is particularly true for the peripheral and coronary circulations. Readers will appreciate this better from Dintenfass' book on clinical hemorheology. The author has written this book for practicing physicians. The book contains discussion of hemodynamic phenomena of rheology in ischemic heart disease, sickle cell anemia and other hematologic disease states, senility and various hyperviscosity states of the blood. This book is excellent. It focuses attention on aspects of the circulation that require much more attention, such as the role of viscosity in renal disease. Maybe the anemia associated with renal disease is advantageous. This reviewer thinks the low viscosity of anemic blood could be a definite advantage under certain circumstances. Thus with further thought, readers can advance their therapeutic considerations of disease states in their patients. The bibliographies are very good. Dintenfass has added an important book to the medical literature. This book is highly recommended to all trainees in medicine, especially those training in the cardiovascular fields.

**The Essentials of Cardiac Pacing** By G Fontaine, Y Grosgeat and J J Welti London 1977 William Heinemann Medical Books Ltd 77 pages

This relatively inexpensive paperback book on pacing presents in simple and lucid manner the problems of cardiac pacing. The illustrations are simple and clear. The presentation is intended for physicians, nurses and other attendants who are involved in the CCU and cardiac programs of hospitals. The translation from French to English is not only good but welcome since the book will reach many more readers. Indications, techniques, complications, functional problems, prognosis and follow-up procedures are among the many phases of cardiac pacing discussed. This is a good and concise book on the subject. It is easy to read and obviously written by experienced French physicians.

**Acute Myocardial Infarction: Reaction and Recovery** By Rue L. Cromwell Ph.D., Earl C. Butterfield Ph.D., Frances M. Brayfield M.A. and John J. Curry M.D. Saint Louis 1977 The C.V. Mosby Company 224 pages Price \$10.50

Cromwell and associates have produced a book of little over 200 pages for nurses, doctors and others concerned with the care of patients with acute myocardial infarction. The psychological impact that this acute medical emergency has on the sufferer is too often forgotten by the busy attendants. Certainly a well trained and experienced physician is aware of his patient's reaction to his illness, but others too often fail to

realize this aspect of the care of the patient. The complex equipment of the CCU demands so much attention that the patient receives inadequate attention and concern for his psychologic state and reaction to the illness and his surroundings. This book discusses the importance of the patient's psyche and reviews the results of studies of the patient's response to doctors, nurses and other attendants as well as to his surroundings. The psychologic assessment of the coronary patient and the manner of coping with his reactions to the CCU, the apparatus and people are reviewed. The study was conducted in large part at the Holy Cross Hospital in Silver Spring, Maryland, with John Curry providing the cardiologic support. This is an interesting book for nurses and trainees in medicine. Even the well trained experienced physician should find the investigations and recommendations interesting and stimulating, even though a great deal is already well known to him.

**Patient Care in Cardiac Surgery** second edition By Douglas M. Behrendt MD and W. Gerald Austen MD. Boston 1976 Little Brown & Company 179 pages

This is a very useful condensed source of practical information concerning the care of the cardiac surgical patient. The advancements in complex cardiac surgery have introduced equally complex and important procedures and practices related to preoperative, operative and postoperative care of the cardiac surgical patient. This small book describes in a brief manner the essentials for the surgical care of adults and children undergoing operations on the heart. The illustrations are well chosen and clear. The use of outlines, tables and charts is a good feature of this book. The authors emphasize their own experience and include those of others. Cardiologists who participate in the care of cardiac surgical patients will find the book informative and a fine and helpful source of information on drugs as well as procedures. This second edition is highly recommended to cardiologists as well as to cardiac surgeons.

**Infections of Prosthetic Heart Valves and Vascular Grafts** Edited by Richard J. Duma. Baltimore 1977 University Park Press 352 pages Price \$26.50

This book represents the proceedings of a conference held in Richmond, Virginia during March 1976. The papers in this volume review rather extensively the many problems related to infections of prosthetic valves and vascular grafts. Etiology, morbidity, mortality, pathology, bacteriology, diagnosis, portals of entry, therapy, surgical management and prevention are thoroughly reviewed for the clinician. This subject is important and is a common problem. This reviewer's experience finds diagnosis is made late and management is not of the best. Any patient with a prosthetic valve or a graft is prone to infection of these prostheses. With early and proper treatment the results should be good. Clinicians who care for patients with artificial valves and plastic grafts will find this to be a valuable book. The discussions are good and the bibliography rather extensive.

## Books received

---

Quality Control in Nuclear Medicine: Radiopharmaceuticals, Instrumentation and In Vitro Assays. Edited by Buck A. Rhodes. St. Louis, 1977. The C. V. Mosby Company. 455 pages. Price \$39.50.

Local Anesthetics. 2nd edition. By Rudolph H. de Jong. M.D. Springfield, Ill., 1977. Charles C. Thomas Publisher. 279 pages. Price \$32.50.

Pathophysiology and Therapeutics of Myocardial Ischemia. Edited by Allan M. Lefer, Gerald J. Kellihier, and Michael J.

Rovetto. Jamaica, N. Y., 1977. Spectrum Publications, Inc. 530 pages. Price \$38.50.

The Prostaglandins, vol. 3. Edited by Peter W. Ramwell. New York, 1977. Plenum Publishing Corp. 347 pages. Price \$39.50.

Guide to Fitness after 50. Edited by Raymond Harris, M.D., and Lawrence J. Frankel. New York, 1977. Plenum Publishing Corp. 338 pages. Price \$14.50.

**Rheology of Blood in Diagnostic and Preventive Medicine** By Leopold Dintenfass London 1976 Butterworth & Co Ltd 396 pages Price \$27.95

Physicians including cardiologists and vascular physicians and surgeons give relatively little consideration to rheology of blood. They fail to even realize the importance of blood viscosity in peripheral blood flow. The hydraulic and hemodynamic aspects of the circulation must be borne in mind constantly when treating patients with cardiovascular disease. This is particularly true for the peripheral and coronary circulations. Readers will appreciate this better from Dintenfass' book on clinical hemorheology. The author has written this book for practicing physicians. The book contains discussion of hemodynamic phenomena of rheology in ischemic heart disease, sickle cell anemia and other hematologic disease states, senility and various hyperviscosity states of the blood. This book is excellent. It focuses attention on aspects of the circulation that require much more attention such as the role of viscosity in renal disease. Maybe the anemia associated with renal disease is advantageous. This reviewer thinks the low viscosity of anemic blood could be a definite advantage under certain circumstances. Thus with further thought readers can advance their therapeutic considerations of disease states in their patients. The bibliographies are very good. Dintenfass has added an important book to the medical literature. This book is highly recommended to all trainees in medicine especially those training in the cardiovascular fields.

**The Essentials of Cardiac Pacing** By G Fontaine, Y Grosgeat and J J Weltz London 1977 William Heinemann Medical Books Ltd 77 pages

This relatively inexpensive paperback book on pacing presents in simple and lucid manner the problems of cardiac pacing. The illustrations are simple and clear. The presentation is intended for physicians, nurses and other attendants who are involved in the CCU and cardiac programs of hospitals. The translation from French to English is not only good but welcome since the book will reach many more readers. Indications, techniques, complications, functional problems, prognosis and follow up procedures are among the many phases of cardiac pacing discussed. This is a good and concise book on the subject. It is easy to read and obviously written by experienced French physicians.

**Acute Myocardial Infarction: Reaction and Recovery** By Rue L. Cromwell, Ph.D., Earl C. Butterfield, Ph.D., Frances M. Bravfield, M.A. and John J. Curry, M.D. Saint Louis 1977 The C.V. Mosby Company 224 pages Price \$10.50

Cromwell and associates have produced a book of little over 200 pages for nurses, doctors and others concerned with the care of patients with acute myocardial infarction. The psychologic impact that this acute medical emergency has on the sufferer is too often forgotten by the busy attendants. Certainly a well trained and experienced physician is aware of his patient's reaction to his illness but others too often fail to

realize this aspect of the care of the patient. The complete equipment of the CCU demands so much attention that the patient receives inadequate attention and concern for his psychologic state and reaction to the illness and his surroundings. This book discusses the importance of the patient's psyche and reviews the results of studies of the patient's response to doctors, nurses and other attendants as well as to his surroundings. The psychologic assessment of the coronary patient and the manner of coping with his reactions to the CCU, the apparatus and people are reviewed. The study was conducted in large part at the Holy Cross Hospital in Silver Spring, Maryland, with John Curry providing the cardiologic support. This is an interesting book for nurses and trainees in medicine. Even the well trained experienced physician should find the investigations and recommendations interesting and stimulating even though a great deal is already well known to him.

**Patient Care in Cardiac Surgery** second edition By Douglas M. Behrendt, M.D. and W. Gerald Austen, M.D. Boston 1976 Little Brown & Company 179 pages

This is a very useful condensed source of practical information concerning the care of the cardiac surgical patient. The advancements in complex cardiac surgery have introduced equally complex and important procedures and practices related to preoperative, operative and postoperative care of the cardiac surgical patient. This small book describes in a brief manner the essentials for the surgical care of adults and children undergoing operations on the heart. The illustrations are well chosen and clear. The use of outlines, tables, and charts is a good feature of this book. The authors emphasize their own experience and include those of others. Cardiologists who participate in the care of cardiac surgical patients will find the book informative and a fine and helpful source of information on drugs as well as procedures. This second edition is highly recommended to cardiologists as well as to cardiac surgeons.

**Infections of Prosthetic Heart Valves and Vascular Grafts** Edited by Richard J. Duma, Baltimore 1977 University Park Press 352 pages Price \$26.50

This book represents the proceedings of a conference held in Richmond, Virginia during March 1976. The papers in this volume review rather extensively the many problems related to infections of prosthetic valves and vascular grafts. Etiology, morbidity, mortality, pathology, bacteriology, diagnosis, portals of entry, therapy, surgical management and prevention are thoroughly reviewed for the clinician. This subject is important and is a common problem. This reviewer's experience finds diagnosis is made late and management is not of the best. Any patient with a prosthetic valve or a graft is prone to infection of these prostheses. With early and proper treatment the results should be good. Clinicians who care for patients with artificial valves and plastic grafts will find this to be a valuable book. The discussions are good and the bibliographies rather extensive.

## Editorial

### Natural fibrinolysis

Norman L Browse MD FRCS (Eng)  
London England

When prehistoric man cut himself and saw the cut seal up with congealed blood he probably appreciated that this was a life saving property of the blood but thousands of years passed before Morgagni and Hunter<sup>1</sup> observed that there was a natural system in the blood which could prevent its coagulation. The intricacies of the coagulation mechanism have been gradually unravelled over the past three decades but we have been far less successful in expanding our knowledge of the fibrinolytic system. In 1937 Macfarlane<sup>2</sup> demonstrated that test tube thrombi made from blood taken during surgical operations sometimes dissolved spontaneously and in 1953 Fearnley and Tweed showed that there was some fibrinolytic activity in the blood of patients at rest. At the same time Mole<sup>3</sup> and Kwaan and McFadzean<sup>4</sup> developed the hypothesis that the vascular endothelium was the main source and store of fibrinolytic activator which was confirmed when Todd<sup>5</sup> demonstrated an activator of fibrinolysis in the walls of small blood vessels; particularly the veins and Astrup showed that there are plasminogen activators in almost all of the fluids and tissues of the body.

As our knowledge has progressed two hypotheses have developed. The first is that fibrinolysis exists as a counterbalance to thrombosis by dissolving the many small thrombi which may

develop in the circulation and so keeping the blood liquid. The second is that an abnormality of natural fibrinolysis might predispose towards intravascular thrombotic disease particularly in the veins or exacerbate the deposition of fibrin in atherosclerosis and any other condition associated with a fibrinous exudate.

Hard evidence that fibrinolysis and coagulation maintain a balance which keeps the blood liquid is circumstantial and sparse. There is no doubt that both systems exist and that abnormality of one or the other leads to pathological states but no one has clearly demonstrated a continual intravascular deposition of fibrin which is continually being dissolved by fibrinolysis.

The association between a deficiency of fibrinolysis and vascular disease is becoming more apparent. After Fearnley's original studies of natural fibrinolysis he searched for drugs which might enhance fibrinolytic activity and found that the combination of an hypoglycemic drug such as phenformin and an anabolic steroid such as ethylestranol would produce long term enhancement of blood fibrinolytic activity.<sup>6</sup> He postulated that these drugs might be used for the treatment of arterial venous and inflammatory diseases. In Malmö Inga Marie Nilsson and co-workers<sup>7,8</sup> extended these studies and showed that there was an abnormality of tissue fibrinolytic activator in patients with venous thrombosis and that recurrent thrombosis associated with an abnormality of fibrinolysis could be prevented by pharmacological fibrinolytic enhancement.

Browse and associates<sup>9</sup> at St Thomas Hospi-

From the Department of Surgery St Thomas Hospital Medical School, London E 8 6JL.

Received for publication June 18, 1977.

Reprint requests: Norman L. Browse MD, Dept of Surgery St Thomas Hospital Medical School, London SE1 7EJ.

## **William Harvey 400th Anniversary Celebration**

A conference celebrating the 400th anniversary of the birth of William Harvey will be held July 9 through 13 1978 at the Royal College of Physicians of London This conference will include a two and a half day symposium entitled *Modern Methods of Studying the Circulatory System* For further information regarding this conference please contact Conference Secretary Harvey Celebration 1978 Royal College of Physicians Regents Park London NW1 4LE England

## **Fifth European Congress of Anesthesiology**

The Fifth European Congress of Anesthesiology entitled *Hemodynamics in Anesthesia and Intensive Care* will be held in Paris France on September 4 through 9 1978 in the

Palais des Congrès For further information regarding the congress please write *Congrès Anesthésie-PMV BP 918 92205 Neuilly Sur Seine France*

## **Information for authors**

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published Authors will be consulted when possible regarding republication of their material

- M Blood and vein wall fibrinolytic activity in health and vascular disease *Br Med J* 14:8 1977
- 13 Jarrett P E M Morland M and Browne N L. Idiopathic recurrent superficial thrombophlebitis Treatment with fibrinolytic enhancement *Br Med J* 2 933 1977
- 14 Burnand K G Clemenson G Whimster I and Browne N L Extravascular fibrin deposition in response to venous hypertension—the cause of venous ulceration *Br J Surg* 63 660 1976
- 15 Jarrett P E M Burnand K G Morland M., and Browne N L. Fibrinolysis and fat necrosis of the lower leg, *Br J Surg* 63 157 1976
- 16 Lack C H. Proteolytic activity and connective tissue *Br Med Bull* 20 917 1964



tal London have recently published a review of a large series of patients with various forms of vascular disease which suggests that there are two degrees of natural fibrinolytic activity. Arm vein blood from patients with atherosclerosis, Raynaud's syndrome secondary to scleroderma, or a past history of deep vein thrombosis has a depressed fibrinolytic activity but a normal level of activity after ten minutes of venous congestion, whereas blood from patients with idiopathic recurrent superficial thrombophlebitis or post phlebotic lipodermatosclerosis has depressed activity at rest and after venous congestion.

These workers have also conducted a number of clinical trials of fibrinolytic enhancement which appears to confirm the hypothesis that some of these diseases or their symptoms are due to the abnormality of blood fibrinolytic activity, because the correction of the blood abnormality has cured the symptoms. For example, in 16 patients with idiopathic recurrent superficial thrombophlebitis the remission of symptoms was directly related to the correction of blood activity.<sup>13</sup> This variety of recurrent thrombosis was studied rather than deep vein thrombosis because it is very difficult to be certain whether patients who have had a deep vein thrombosis and then get recurrent episodes of pain and discomfort are actually having recurrent thrombosis, whereas attacks of superficial thrombophlebitis are easy to see and measure.

Perhaps more interesting than the response of the patients with superficial thrombophlebitis is the response of the patients with post phlebotic lipodermatosclerosis. The St Thomas group have shown that the changes in the skin and subcutaneous tissues which often accompany damage to the calf muscle pump is probably caused by the deposition of fibrin in the pericapillary spaces which by forming an impervious cuff stops oxygen diffusion to the tissues and ultimately causes tissue necrosis i.e., venous ulceration.<sup>14</sup> In a small pilot study on 14 patients, presented in a preliminary communication to the Surgical Research Society the enhancement of these patients' depressed blood fibrinolytic activity with the anabolic steroid stanozolol produced considerable relief of symptoms and a reduction of the area of tenderness, redness, induration and pigmentation.<sup>15</sup> A double blind cross over trial not yet published has confirmed these results. The significant point is that the enhancement of

fibrinolysis in these patients appears to be affecting an extravascular abnormality. This forces one to consider the possibility that a low level of blood fibrinolytic activity may be an indication of a defect of tissue fibrinolysis and not necessarily a primary blood abnormality. It may be that one of the important functions of fibrinolysis is to keep the tissues rather than the blood vessels clear of unwanted protein such as fibrin. It is not a new suggestion that there may be tissue clearing proteolytic enzymes.<sup>16</sup> If this is the case and if what we measure in the blood and call natural fibrinolysis is simply the spill over of tissue fibrinolytic activity, we must review the hypothesis that the primary role of fibrinolysis is to counterbalance coagulation.

All these theories need further detailed investigation after we have refined our methods of measuring blood and tissue fibrinolytic activity. But more pressing is the need for new drugs which will produce a greater enhancement of fibrinolytic activity and which are safe for long term administration. If such drugs were available we might be able to cure patients with recurrent venous thrombosis, enhance the spontaneous resolution of thrombosis and perhaps reduce the complications of arterial disease by reducing the quantity of fibrin that is laid down in and around atherosclerotic plaques.

#### REFERENCES

- 1 Morgagni J B. De sedibus et causis morbum per anatomen indagatis. Venice 1769.
- 2 Hunter J A. Treatise on the blood inflammation and gunshot wound. London 1794.
- 3 Macfarlane R G. Fibrinolysis following operation. *Lancet* 1 10 1937.
- 4 Fearnley G H and Tweed J M. Evidence of an active fibrinolytic enzyme in the plasma of normal people. *Clin Sci* 12 81 1953.
- 5 Mole R H. Fibrinolysis and the fluidity of the blood post mortem. *J Pathol Bacteriol* 60 413 1948.
- 6 Kwaan H C and McFadzean A J S. On plasma fibrinolytic activity induced by ischaemia. *Clin Sci* 15 245 1956.
- 7 Todd A S. Histological localisation of fibrinolysis activator. *J Pathol Bacteriol* 78 281 1959.
- 8 Astrup T. The biological significance of fibrinolysis. *Lancet* 2 565 1956.
- 9 Fearnley G H, Chakrabarti R and Hocking E D. Fibrinolytic effects of Digoxinides & Ethylestradiol in occlusive vascular disease. *Lancet* 2 1008 1967.
- 10 Nilsson I M and Isacson S. New aspects of the pathogenesis of thromboembolism. *Prog Surg* 11 46 1973.
- 11 Hedner V, Nilsson I M and Isacson S. Effect of ethylestradiol on fibrinolysis in the vessel wall. *Br Med J* 3 729 1976.
- 12 Browne N L, Gray L, Jarrett P E M and Morland

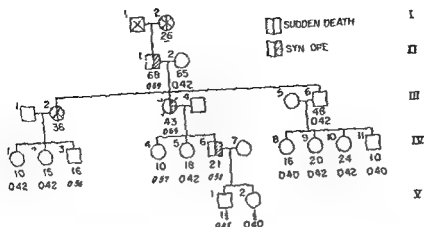


Fig 1 Family pedigree. The subjects' age in years and Q T interval in seconds are shown beneath their symbol. Abnormal Q T intervals are indicated in italics.

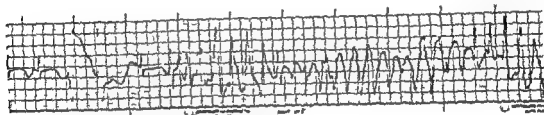


Fig 2 Coronary care unit rhythm strip in proband III 3 showing onset of ventricular tachycardia which eventually resulted in a typical syncope episode.

hereditary disorder disclosed no significant abnormalities suggestive of a cause of death. Her son IV 6 has experienced multiple syncope episodes since age 6. His Q T interval and that of one of his children is abnormally prolonged. Two other family members are affected but asymptomatic—her nephew IV 3 and her daughter IV 4. Her brother III 6 and his four children are unaffected and asymptomatic.

Estimation of serum potassium, magnesium, and calcium values in all living family members were within normal limits.

## Methods

Informed consent was obtained from all subjects. Three affected family members were studied. Two were symptomatic: II 1 age 68 and IV 6 age 20, and one was asymptomatic: IV 3 age 16. A pool of five male and three female volunteers ages 24 to 39 years served as control subjects. Four unaffected family members: IV 1, IV 2, IV 9, and IV 11 were given atropine and propranolol as described below. No subject was receiving any medication at the time of study.

The study was carried out on two successive days. On the first study day the subjects were brought to the laboratory at 8 AM in the preprandial state. In the supine position the

following maneuvers were performed: (1) manual right and then left carotid sinus stimulation for 7 seconds; (2) Valsalva maneuver with the subject expiring against an aneroid manometer to maintain a constant pressure of 30 mm Hg for 15 seconds; (3) sustained handgrip at 30 per cent of maximal tension for 3 minutes; (4) maximal treadmill exercise using a modified Bruce protocol consisting of 3 minute stages. After the heart rate was constant for 15 minutes, propranolol hydrochloride was given by intravenous bolus injection in a dosage of 0.15 mg/Kg, and the above maneuvers were repeated usually in the course of one half hour. Atropine was then administered as a bolus injection in a dosage of 0.035 mg/Kg. The maneuvers were again repeated with the exception of treadmill exercise for the affected family members. On the second study day the isoproterenol hydrochloride infusion rate (1 mg/1000 cc) required to increase the resting heart rate by 30 cycles/minute was determined. After return to the baseline heart rate the previously calculated dose of atropine was given by intravenous bolus injection and the

## Autonomic maneuvers in hereditary Q-T interval prolongation (Romano-Ward syndrome)

Edward I. Curtiss, MD, FACC

Richard H. Heibel, MD\*

James A. Shaver, MD, FACC

Pittsburgh, Pa

The syndromes associated with hereditary Q-T interval prolongation are characterized by a family history of sudden death and syncopal episodes due to paroxysmal ventricular arrhythmias.<sup>1-11</sup> When associated with congenital deafness and autosomal recessive inheritance, it is known as Jervell-Lange-Nielsen syndrome<sup>1</sup> when the pattern of inheritance is autosomal dominant and no deafness is present, the syndrome is termed Romano-Ward.<sup>12</sup>

The relative rarity of these syndromes has rendered it difficult to conduct systematic investigations of etiologic mechanisms. At the present time, asymmetric stimulation of the heart via the right and left sympathetic chains appears to hold the most promise as a primary etiologic factor. Evidence for this hypothesis includes experimental studies in dogs by Yanowitz and colleagues<sup>13</sup> showing prolongation of the Q-T interval by right stellate ganglionic section or left stellate stimulation associated with predominant prolongation of functional refractory period over the anterior ventricular surface, amelioration of pharmacologically intractable ventricular arrhythmias in affected patients by left stellectomy,<sup>11, 12, 14</sup> and the putative efficacy of beta adrenergic blockade in alleviating symptoms in affected subjects.<sup>7, 11, 15</sup>

From the Division of Cardiology, University of Pittsburgh School of Medicine and Presbyterian University Hospital, Pittsburgh, Pa. Supported in part by Grant No. 5T01 HL-05678-10 from the National Heart and Lung Institute.

Received for publication Oct. 13, 1976.

Accepted for publication Jan. 6, 1977.

Reprint requests: Edward I. Curtiss, MD, Director, Central Heart Station, Presbyterian University Hospital, Pittsburgh, Pa. 15213.

This study was performed during Dr. Richard Heibel's tenure as a Fellow in Cardiology.

Since it appears likely that asymmetric sympathetic stimulation should result from a relative predominance of left chain sympathetic activity, its genesis may lie in either increased left or decreased right sided stimulation. Schwartz and co-workers<sup>11</sup> in a recent review of the literature have proposed the latter is suggested by the many reports of resting sinus bradycardia and exercise induced Q-T interval prolongation and some reports of decreased or absent heart rate increments with exercise and atropine administration.

Since systematic employment of autonomic maneuvers and autonomically active drugs might serve to uncover autonomic dysfunction in hereditary Q-T prolongation, we undertook such a study in a family with Romano-Ward syndrome.

### Family history

The proband (III-3) (Fig. 1) is a 43-year-old white female with a 12-year history of syncopal episodes. These episodes were the result of paroxysmal ventricular tachycardia and fibrillation (Fig. 2). During sinus rhythm the Q-Tc was abnormally prolonged to 0.69 seconds. Cardiac catheterization studies including selective coronary arteriography disclosed no abnormalities. Sequential blockade of the right and left stellate ganglia by percutaneous lidocaine infiltration was sufficient to produce an appropriate ipsilateral Horner's syndrome but resulted in no alteration of Q-T interval. The patient was placed on propranolol with an initial decrease in syncopal episode frequency; after eight months, however, the frequency increased necessitating substitution of propranolol by procainamide.

Sudden death, syncope, or abnormal Q-T interval prolongation was found in five generations of her family. Her grandmother died suddenly at the age of 26. The father (II-1) had multiple syncopal attacks since age 64 and manifests Q-T interval prolongation. Her sister (III-2) died suddenly at age 30, preceded by two months of recurrent syncopal episodes. Postmortem examination conducted without knowledge of a

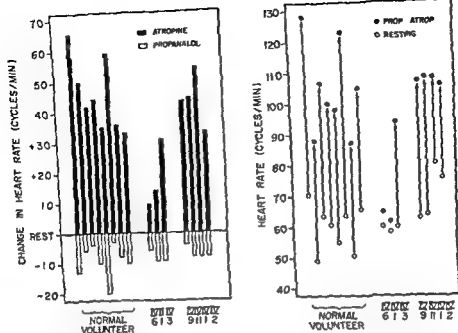


Fig 4 Left hand panel heart rate responses to propranolol and atropine in normal volunteers, affected (II 1 and IV 3) and unaffected (II 9 IV 11 IV 1 IV 2) family members. The atropine heart rate increment is abnormally reduced in the symptomatic family members (II 6 IV 1). Right hand panel resting and intrinsic (propranolol plus atropine) heart rates in the above subjects. The latter rate is abnormally low in the symptomatic family members.

mean increment in heart rate from the beginning of Stage II to the end of exercise was 80 cycles/minute in the normal volunteers and not appreciably different for the affected family members. Following beta adrenergic blockade the maximal heart rate achieved and above heart rate increment were significantly depressed in the normal volunteers. However the corresponding values were significantly lower in all the affected family members. The low increments were not related to a higher heart rate at the onset of Stage II nor to any difference in exercise duration from the control state. In the normal volunteers the maximal heart rate achieved following propranolol plus atropine was  $4 \pm 8$  (SD) cycles/minute greater than that observed during beta adrenergic blockade alone; this difference was not statistically significant (paired data).

Following beta adrenergic blockade in the normal volunteers decrements in resting heart rate ranged from 3 to 20 cycles/minute and were not appreciably different in the affected and unaffected family members (Fig 4 left hand panel). However following atropine administration the increment in heart rate was grossly abnormally small in the two symptomatic patients. The mean heart rate increment in the normal volunteers was 46 cycles/minute

(range 33 to 66) in II 1 and IV 6 the observed values were 14 and 9 cycles/minute respectively. As compared to the volunteers the atropine increment was also depressed when parasympathetic blockade was preceded by beta adrenergic blockade.

The abnormally low heart rate increment with atropine in the two symptomatic subjects was not related to elevated resting heart rates. All three affected family members tended to have low resting heart rates averaging 61, 63 and 60 cycles/minute for II 1, IV 3 and IV 6 respectively. The intrinsic heart rate or the heart rate recorded five minutes after combined beta adrenergic and parasympathetic blockade was significantly depressed in the symptomatic members (Fig 4 right hand panel). The observed values of 58 and 64/minute were 10 and 27 cycles/minute below the lower limit of normal expected on the basis of age. Control left ventricular systolic time intervals of the symptomatic family members were well within normal limits and after combined blockade their PEP/LVET ratios were similar to that found in normal volunteers. In addition the heart rate observed after ganglionic blockade was abnormally low (Fig 5). For II 1 and IV 6 the values observed were 64 and 63 cycles/minute in normal volunteers previously studied in our labo-

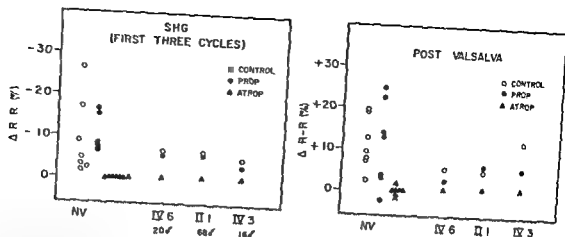


Fig 3 Heart rate responses to sustained hand grip (SHG left panel) and Valsalva release in the normal volunteers (NV) and affected family members. Atrop = atropine Prop = propranolol

Table 1 Maximal treadmill exercise

|                                | Heart rate<br>(cycles/min)<br>maximal | Heart rate<br>(cycles/min)<br>increment from<br>stage II onset<br>to termination |
|--------------------------------|---------------------------------------|--|
| <b>Normal volunteers</b>       |                                       |  |
| Control mean                   | 188                                   | +50  |
| Range                          | 174-201                               | 6-102  |
| + Propranolol mean             | 155                                   | +58  |
| Range                          | 147-180                               | 41-63  |
| % Decrease + mean              | 17                                    | 26   |
| Range                          | 10-21                                 | 9-42   |
| <b>Affected family members</b> |                                       |  |
| Control                        | 175-170-188                           | +76-77-97  |
| IV 6 II 1 IV 3                 |                                       |  |
| + Propranolol                  | 125-110-125                           | +37-26-35  |
| IV 6 II 1 IV 3                 |                                       |  |
| % Decrease                     | 29-30-34                              | 51-66-64   |
| Control Propranolol/Control    |                                       |  |

above maneuvers including maximal treadmill exercise were repeated. In these studies electrocardiographic Leads I, aV<sub>r</sub>, and V<sub>6</sub> were simultaneously recorded on an Avionics Model 3000 Exerstress Monitor at paper speeds of 25 and 50 mm/sec.

The two symptomatic family members II 1 and IV 6 had additional studies. Trimethaphan camsylate was infused in the supine position sufficient to result in cuff blood pressures of 70 mm systolic in order to determine heart rate and Q-T interval responses. Left ventricular systolic time intervals were obtained in the control state and after combined beta adrenergic and parasympathetic blockade; these results were compared to those of normal volunteers previously studied in our laboratory.<sup>14</sup>

The lower limit of normal for intrinsic heart

rates (the heart rate observed after administration of atropine and propranolol) based upon age were determined according to the regression equations of Jose and associates.<sup>1</sup>

## Results

Each of the affected family members responded to carotid sinus stimulation (minimum sinus cycle length prolongation of 17 per cent) without induction of abnormal (> 2 seconds) atrial or ventricular pauses, since carotid sinus stimulation was a gross maneuver no quantitative comparisons were attempted.

Vagal withdrawal during sustained handgrip was assessed by comparing the mean value for the first three cycle lengths immediately following onset to the three cycle lengths immediately prior to the institution of isometric exercise. The results are shown in Fig 3 left hand panel. Each subject showed the expected decrease in cycle length which was abolished by atropine but not by propranolol. The parasympathetically induced bradycardic response to Valsalva release is shown in Fig 3 right hand panel. Again each subject showed an appropriate response abolished by atropine but not by propranolol.

During sustained handgrip in the normal volunteers the decrement in sinus cycle length from 1/2 to 3 minutes averaged 8 per cent (range 2 to 16 per cent); the decrease was abolished in each subject after propranolol administration. In the control state the decrement was 9 per cent, 9 per cent, and 12 per cent for II 1, IV 6, and IV 3 respectively, and was similarly abolished by beta adrenergic blockade.

In the control state each subject reached at least 90 per cent of their predicted maximal heart rate during treadmill exercise (Table 1). The

hereditary Q T interval prolongation a disorder in which autonomic dysfunction might play a primary role. Schwartz and colleagues<sup>11</sup> have recently called attention to multiple reports of low resting heart rates in affected individuals and to failure of exercise to increase heart rate in six of twelve subjects where such studies were performed. The responses to partially blocking doses of atropine have been reported in three individuals one of whom failed to increase his heart rate.<sup>12</sup> These findings are of interest since Q T interval and T wave changes analogous to those found in the hereditary Q T interval prolongation syndromes have been produced in experimental animals by right stellate ganglionic section and left stellate ganglionic stimulation.<sup>13</sup> The heart rate responses described above are compatible with decreased sympathetic stimulation presumably through the right stellate ganglion which in dog experiments by Randall and Rohse<sup>14</sup> has been shown to be the primary effector of chronotropic actions.

In the family forming the basis of the current report isotonic and isometric exercise yielded no appreciable abnormalities of heart rate responses in the control state. However similar to the report of Pernot and associates<sup>4</sup> the two symptomatic family members evidenced abnormally depressed heart rate increments in response to atropine administration. This could not solely be attributed to a defect in resting sympathetic stimulation as the response was depressed both with and without prior beta adrenergic blockade. A high degree of resting vagal withdrawal is unlikely in view of resting heart rates in or near the bradycardic range and the ability to demonstrate such withdrawal during sustained hand grip. Hypersensitivity to vagal stimuli as may be encountered in sick sinus syndrome<sup>15</sup> is also unlikely considering the normal responses to carotid sinus pressure and Valsalva release and the use of atropine dosages sufficient to insure complete parasympathetic blockade.<sup>16</sup> A defect in sinus node automaticity tended to be excluded by their response to isoproterenol infusion.<sup>14</sup>

The abnormally low increments with atropine in the sympathetic family members appear to be related to a depressed intrinsic heart rate. This term has been coined by Jose and co-workers<sup>17, 18</sup> and refers to the resting heart rate found after presumably complete pharmacologic autonomic blockade. In II 1 and IV 5 abnormally low heart

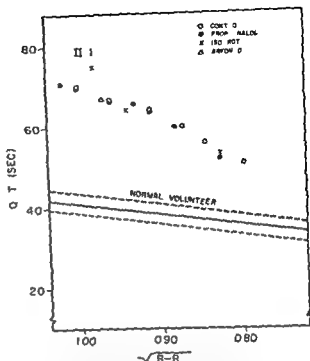


Fig 6 Q T intervals in affected family member II 1. The square root of the cycle length in seconds, is shown on the abscissa and the observed Q T interval on the ordinate. Control and propranolol values were obtained during the recovery from treadmill exercise. Similar control values for the normal volunteers are indicated by the solid regression line. The dashed lines represent two standard deviations. Except for a single isoproterenol value II 1's Q T intervals were not significantly altered by autonomically active drugs. Isoproterenol = isoproterenol.

rates were found after administration of propranolol plus atropine and after ganglionic blockade with trimethaphan. Jose and colleagues<sup>17, 18</sup> found the intrinsic heart rate to be directly related to myocardial contractility and inversely related to age. The low rates observed in our patients were not apparently explicable on either basis. The ability to increase intrinsic heart rate would be reflected in the response to maximal treadmill exercise following beta adrenergic blockade. The normal volunteer data suggest parasympathetic influences are relatively unimportant in determining maximal heart rate responses during isotonic exercise. The low maximal heart rate and subnormal increments in all three affected family members suggest an impaired ability to increase intrinsic heart rate.

Though a low resting intrinsic heart rate was seen only in the symptomatic subjects, its genesis and its relationship to symptomatic manifestations are obscure. It may be related to intrinsic

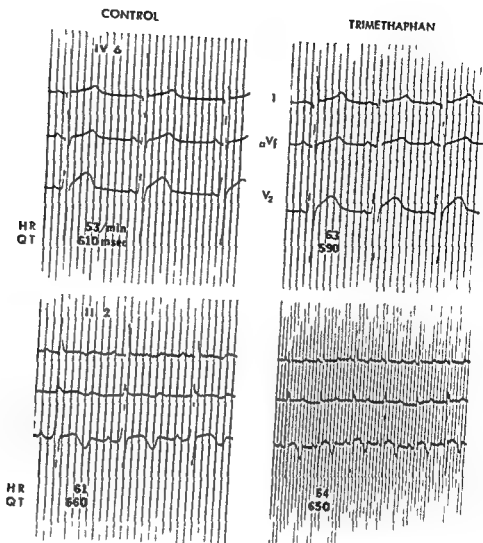


Fig 5 Heart rate and Q T interval responses to trimethaphan a ganglionic blocking agent in the symptomatic family members IV 6 20 years old and II 2 68 years old The findings illustrated during trimethaphan infusion were obtained when the blood pressure had decreased to 70 mm systolic Control blood pressures in IV 6 and II 2 were 120/64 and 130/92 respectively In both subjects the heart rate increment is abnormally decreased and the Q T interval is not altered apart from the change ascribable to the change in cycle length Time lines = 100 msec

ratory, the mean heart rate during trimethaphan infusion was 98/minute (range 73 to 116)

The isoproterenol infusion rate required to increase the resting heart rate by 30 cycles/minute averaged 25.8 ng/Kg/minute (range 11.2 to 37.0) in the normal volunteers These values were not appreciably abnormal for II 1 (26.6 ng/Kg/minute), IV 6 (17.6), and IV 3 (18.2)

The durations of all measurable Q T intervals in the affected family members were prolonged However, as compared to the normal volunteers their intervals tended to decrease at a faster rate with decreasing cycle length Fig 6 shows the Q T intervals plotted against cycle length for subject II 1 The lower line is the regression of Q T interval on cycle length for the normal volunteers during recovery from treadmill exercise it was not significantly affected by propranolol The

regression was also unchanged by propranolol in the affected family members Similar to subject IV 6 II 1's Q T interval was not significantly altered by trimethaphan apart from the change ascribable to the decrease in cycle length However, with the lowest rate of isoproterenol infusion II 1's Q T interval prolonged with a tendency toward alternation in T or U wave amplitude despite an increase in heart rate (Fig 7) As the isoproterenol infusion rate was augmented these changes disappeared, subsequent Q T intervals were not significantly different from the control state

#### Discussion

Autonomic influences on heart rate control in man have been extensively investigated but little information is available on such influences in

of local anesthetic has been reported to produce shortening lengthening " and no change " in Q T interval Since this procedure is performed blindly it may not result in blockade restricted to the ipsilateral stellate ganglion However surgical stellate ganglionectomy under direct vision in two individuals " has resulted in only transient Q T interval shortening Despite subsequent lengthening of the interval in these subjects there was protracted amelioration of symptoms and presumably a decrease in the incidence of ventricular arrhythmias leading to syncope Reduction in arrhythmia frequency may also constitute a non-specific effect since in experimental animals left stellate ablation has been shown to increase ventricular fibrillation threshold " However these findings suggest that even if the effects of alterations in sympathetic tone are non specific further investigation of their role in hereditary Q T interval prolongation is warranted by their potential for indicating beneficial modifications of the therapeutic regimen

Observations in a single family with hereditary Q T interval prolongation obviously cannot be made the basis for broad generalizations concerning the disease itself Our results only suggest some manifestations may have an intrinsic cardiac basis In that regard sinus bradycardia and probably abnormal heart rate responses to exercise cannot be invoked to support an extrinsic autonomic etiology unless an intrinsic defect is specifically excluded

### Summary

Since extrinsic autonomic defects have been postulated to be a primary etiologic mechanism in hereditary Q T interval prolongation heart rate and Q T interval responses of three affected members of a family with Romano Ward syndrome and eight normal volunteers were studied in the control state and after blocking doses of propranolol atropine propranolol plus atropine and trimethaphan a ganglionic blocking agent The isoproterenol infusion rate required to increase resting heart rate by 30 per minute was determined During the control state cycle length changes in the normal volunteers and affected family members were not appreciably different with respect to prolongation during carotid sinus pressure and post Valsalva and shortening during the initial phase of hand grip These changes were abolished by atropine

but not by propranolol As compared to the normal volunteers the affected family members maintained heart rates during treadmill exercise were similar but after propranolol they were significantly lower Isoproterenol sensitivity in affected family members was not significantly different from that in normal volunteers

The affected family members tended to have low resting heart rates and manifested abnormally low increments in rate with atropine Their heart rates were abnormally low after propranolol plus atropine and trimethaphan without evidence of depressed left ventricular function When changes in cycle length were accounted for affected family members Q T intervals during the control maneuvers were unaltered by propranolol trimethaphan and isoproterenol However one affected family member demonstrated disproportionate Q T interval lengthening and alternation in T or U wave amplitude with the lowest isoproterenol infusion rate these changes disappeared as the infusion rate was increased The present study suggests intrinsic cardiac changes are present in this family with Romano Ward syndrome Their relationship to any extrinsic sympathetic defect is unclear

The authors wish to thank Albert Treger M D for permission to study the family Miss Mary Ann Scully for technical assistance and Mrs. Minnie Flansbaum for secretarial assistance

### REFERENCES

1. Jervell A and Lange-Nielsen F Congenital deaf-mutism functional heart disease with prolongation of the Q T interval and sudden death. *AM HEART J* 54: 99, 1955
2. Jervell A Thøgersd R and End Jø T The syndromic deafness three new cases of congenital deafness with syncopal attacks and Q T prolongation in the electrocardiogram. *AM HEART J* 72: 582, 1966
3. Fraser G R Froggatt P and James T N Congenital deafness associated with electrocardiographic abnormalities fainting attacks and sudden death a recessive syndrome. *Q J Med* 131: 361, 1964
4. Romano C Gettone G and Pongiglione R Aritmia cardiache rare dell'età pediatrica. *La Clinica Paed* 45: 636, 1963
5. Romano C Congenital cardiac arrhythmia. *Lancet* 1: 653, 1963
6. Ward H C A new familial cardiac syndrome in children. *J Irish Med Assoc* 54: 103, 1964
7. Garza L A Vick R L Nora J J and McNamara D G Heritable Q T prolongation without deafness. *Circulation* 41: 39, 1970
8. Phillips J and Ichimose H Clinical and pathological studies in the hereditary syndrome of a long Q T interval syncope spells and sudden death. *Chest* 58: 236, 1970
9. Matthews E C, Jr Blount A W Jr and Townsend J I Q T prolongation and ventricular arrhythmias.



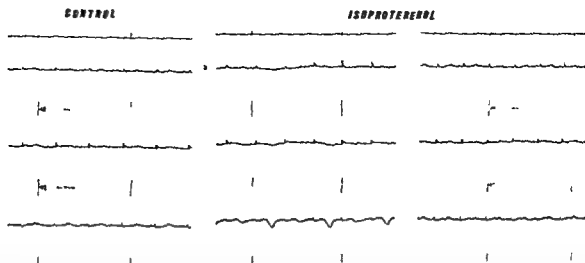


Fig 7 Electrocardiograms in subject II 1 during the control state (first panel) the lowest rate of isoproterenol infusion (second panel) and a higher infusion rate (third panel) During the control state the Q-T interval is 0.65 sec At the lowest isoproterenol infusion rate the Q-T interval prolongs to 0.74 sec despite an increase in heart rate and the T wave alternates in amplitude from cycle to cycle These changes disappear as the isoproterenol infusion rate is increased

sinus node disease as described by Fraser and co-workers<sup>3</sup> and by James in three affected members of a family with Jervell-Lange-Nielsen syndrome. In these subjects postmortem examination revealed medial thickening of the intranodal portion of the sinus node artery, extensive hemorrhage of the nodal-right atrial junction and hemorrhagic or degenerating parasympathetic ganglia near the node. If the etiologic abnormality is indeed anatomic, it is difficult to conceive how it would bear a cause-effect relationship with Q-T prolongation except at a metabolic or cellular level. In the other few affected individuals where postmortem examination has been performed,<sup>1,2,8,9</sup> the sinus node was examined in two instances<sup>8,9</sup> and no histologic abnormalities were found. It is also significant that the atropine heart rate response was apparently abnormal in only one of the three previously reported instances. The heart rate abnormalities, although intrinsic, appear to be concomitantly rather than causally related to Q-T interval prolongation.

In contrast to the observations of other authors,<sup>7,8,10,11</sup> no Q-T interval lengthening either absolute or relative to cycle length was observed following exercise of the affected family members. The Q-T interval tended to appropriately decrease with decreasing cycle length, similar to the response in an affected individual observed by Roy and associates<sup>10</sup> where non-adrenergically mediated increases in heart rate were produced by atrial pacing. Since Q-T

interval tended to decrease at a more rapid rate than normal, it was evident that the patient had to be used as his own control to evaluate interval changes associated with concordant alterations in cycle length. Correction of observed Q-T interval by the usual formula ( $QT/\sqrt{R-R}$ ) could have resulted in apparent shortening by any maneuver which increased heart rate. We did not perform atrial pacing but observed no change in the regression of Q-T interval on heart rate following  $\beta$ -adrenergic blockade. The interval was also not independently affected by blockade at the ganglionic level. These findings suggest an intrinsic cardiac abnormality but do not exclude an additional significant extrinsic autonomic defect. In one of our subjects, disproportionate Q-T interval lengthening and T-wave alternans developed only at a relatively low isoproterenol infusion rate; these findings disappeared as the sympathomimetic infusion rate was increased. Thus, the precise level of sympathetic stimulation may be of great importance in determining maximal Q-T interval prolongation and perhaps maximal risk of sustained ventricular arrhythmias.

While it is clear that changes in sympathetic tone may result in significant symptomatic and/or electrocardiographic alterations in affected individuals, the effects have not been uniform from patient to patient and it is uncertain whether these effects are specifically or non-specifically related to the fundamental disorder producing Q-T interval prolongation. In affected individuals, percutaneous left cervical infiltration

of local anesthetic has been reported to produce shortening lengthening<sup>12</sup> and no change in Q T interval. Since this procedure is performed blindly, it may not result in blockade restricted to the ipsilateral stellate ganglion. However, surgical stellate ganglionectomy under direct vision in two individuals<sup>13</sup> has resulted in only transient Q T interval shortening. Despite subsequent lengthening of the interval in these subjects, there was protracted amelioration of symptoms and presumably a decrease in the incidence of ventricular arrhythmias leading to syncope. Reduction in arrhythmia frequency may also constitute a non-specific effect, since in experimental animals left stellate ablation has been shown to increase ventricular fibrillation threshold.<sup>14</sup> However, these findings suggest that even if the effects of alterations in sympathetic tone are non-specific, further investigation of their role in hereditary Q T interval prolongation is warranted by their potential for indicating beneficial modifications of the therapeutic regimen.

Observations in a single family with hereditary Q T interval prolongation obviously cannot be made the basis for broad generalizations concerning the disease itself. Our results only suggest some manifestations may have an intrinsic cardiac basis. In that regard, sinus bradycardia and probably abnormal heart rate responses to exercise cannot be invoked to support an extrinsic autonomic etiology unless an intrinsic defect is specifically excluded.

### Summary

Since extrinsic autonomic defects have been postulated to be a primary etiologic mechanism in hereditary Q T interval prolongation, heart rate and Q T interval responses of three affected members of a family with Romano Ward syndrome and eight normal volunteers were studied in the control state and after blocking doses of propranolol, atropine, propranolol plus atropine and trimethaphan, a ganglionic blocking agent. The isoproterenol infusion rate required to increase resting heart rate by 30 per minute was determined. During the control state, cycle length changes in the normal volunteers and affected family members were not appreciably different with respect to prolongation during carotid sinus pressure and post Valsalva and shortening during the initial phase of hand grip. These changes were abolished by atropine

but not by propranolol. As compared to the normal volunteers, the affected family members' maximal heart rates during treadmill exercise were similar but after propranolol they were significantly lower. Isoproterenol sensitivity in affected family members was not significantly different from that in normal volunteers.

The affected family members tended to have low resting heart rates and manifested abnormally low increments in rate with atropine. Their heart rates were abnormally low after propranolol plus atropine and trimethaphan without evidence of depressed left ventricular function. When changes in cycle length were accounted for, affected family members' Q T intervals during the control maneuvers were unaltered by propranolol, trimethaphan and isoproterenol. However, one affected family member demonstrated disproportionate Q T interval lengthening and alternation in T or U wave amplitude with the lowest isoproterenol infusion rate. These changes disappeared as the infusion rate was increased. The present study suggests intrinsic cardiac changes are present in this family with Romano Ward syndrome. Their relationship to any extrinsic sympathetic defect is unclear.

The authors wish to thank Albert Treger, M.D., for permission to study the family; Miss Mary Ann Scully for technical assistance; and Mrs. Minnie Flansbaum for secretarial assistance.

### REFERENCES

1. Jennell A and Lange Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q T interval and sudden death. *AM HEART J* 54:59, 1957.
2. Jennell A, Thingstad R and Endsjo T. The sudrocardiac syndrome: three new cases of congenital deafness with syncopal attacks and Q T prolongation in the electrocardiogram. *AM HEART J* 72:582, 1966.
3. Praver G R, Froggatt P and James T N. Congenital deafness associated with electrocardiographic abnormalities, fainting attacks and sudden death: a recessive syndrome. *Q J Med* 131:361, 1964.
4. Romano C, Lemme G and Pongiglione R. Antenne cardiache rare dell'età pediatrica. *La Clinica Ped* 45:656, 1963.
5. Romano C. Congenital cardiac arrhythmia. *Lancet* 1:648, 1966.
6. Ward, D C. A new familial cardiac syndrome in children. *J Inh Med Assoc* 54:103, 1964.
7. Garza L A, Vick R L, Nora J J and McNamara D G. Heritable Q T prolongation without deafness. *Circulation* 41:39, 1970.
8. Phillips J and Ichimura H. Clinical and pathological studies in the hereditary syndrome of a long Q T interval, syncopal spells and sudden death. *Chest* 58:74, 1970.
9. Mathews, E C, Jr, Blount A W Jr and Townsend, J I. Q T prolongation and ventricular arrhythmias.

- with and without deafness in the same family *Am J Cardiol* 29 702 1972
- 10 Roy P R Emanuel R Ismail S A and El Tayeb M H Hereditary prolongation of the Q T interval genetic observation and management in three families with twelve affected members *Am J Cardiol* 37 237 1976
- 11 Schwartz P J Pentz M and Malliani A The long Q T syndrome *Am Heart J* 89 378 1976
- 12 Yanowitz F Preston J B and Abildskov J A Functional distribution of right and left stellate innervation to the ventricles production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone *Circ Res* 18 416 1966
- 13 Moss A and McDonald J Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long Q T interval syndrome *N Engl J Med* 285 903 1971
- 14 Schwartz P J and Malliani A Electrical alternation of the T wave clinical and experimental evidence of its relationship with the sympathetic nervous system and the long Q T syndrome *Am Heart J* 89 45 1975
- 15 Olley P M and Fowler R S The surdo cardiac syndrome and therapeutic observations *Br Heart J* 32 467 1970
- 16 Leon D F Shaver J A and Leonard J J Reflex heart rate control in man *Am Heart J* 80 729 1970
- 17 Martin C E Shaver J A Leon D F Thompson M E Reddy P S and Leonard J J Autonomic mechanisms in hemodynamic responses to isometric exercise *J Clin Invest* 54 104 1974
- 18 Shaver J A Gorlin R and Paley H W Ganglionic blockade and left ventricular response to exercise (Abstr) *Fed Proc* 24 146 1965
- 19 Jose A D and Collison D The normal range and determinants of the intrinsic heart rate in man *Cardiovasc Res* 4 160 1970
- 20 Pernot C Henry M and Aigle J C Syndrome cardioauditif de Jervell et torsades de pointes *Arch Mal Coeur* 65 261 1972
- 21 Randall W C and Rohse W G The augmentor action of the sympathetic cardiac nerves *Circ Res* 44 1956
- 22 Mandel W J Hayakawa H Allen H N, Danz R, and Kermaier A J Assessment of sinus node function in patients with the sick sinus syndrome *Circulation* 46 761 1972
- 23 Jose A D and Taylor R R Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man *J Clin Invest* 48 2019 1969
- 24 Strauss H C Bigger J T Jr Saroff A L and Giardina E G V Electrophysiologic evaluation of sinus node function in patients with sinus node dysfunction *Circulation* 53 763 1976
- 25 Jose A D Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man *Am J Cardiol* 18 476 1966
- 26 Jose A D and Stitt F Effects of hypoxia and metabolic inhibitors on the intrinsic heart rate and myocardial contractility in dogs *Circ Res* 25 53, 1969
- 27 James T N Congenital deafness and cardiac arrhythmias *Am J Cardiol* 19 627 1967
- 28 Green J R Korovetz M J Shanklin D R DeVito J J and Taylor W J Sudden unexpected death in three generations *Arch Intern Med* 124 359 1969
- 29 Vincent G M Abildskov J A Burgess M J and Muller K Autonomic manipulation in the inherited long Q T recurrent syncope syndrome (Abstr) *Am J Cardiol* 33 174 1974
- 30 Ratshun R A Hunt D Russell R O Jr and Backley C E QT interval prolongation paroxysmal ventricular arrhythmias and convulsive syncope *Ann Intern Med* 75 914 1971
- 31 Kolman B Verner R L and Lown B The effect of vagus nerve stimulation upon vulnerability of the canine ventricle role of sympathetic-parasympathetic interactions *Am J Cardiol* 37 1041 1976
- 32 Schwartz P J Snebold N G and Brown A M Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold *Am J Cardiol* 37 1034 1976

# Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. P O Box 765 Schenectady N Y 12301 518 371-4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes, for creating new collective works or for resale.

# Significance of new Q waves after bypass grafting

## Correlations between graft patency, ventriculogram and surgical venting technique

Agop Aintablian M D  
Robert I Hamby M D  
Irwin Hoffman M D  
Daniel Weisz M D  
Choudary Voleti M D  
B George Wisoff M D

*Neu Hyde Park Jamaica and Stony Brook N Y*

New postoperative electrocardiographic Q waves have been described in eight to 40 per cent of patients undergoing bypass grafting for coronary artery disease.<sup>1</sup> Various theories have been proposed to explain these new Q waves. Correlations of new Q waves to vein bypass occlusion, prolonged pump time or aortic cross clamping time are controversial.<sup>2-4</sup> Indeed whether or not the appearance of new postoperative Q waves means real transmural myocardial infarction is not clear. We report herein our experience with postoperative Q waves in 56 patients with vein bypass grafts and the relationship of new Q waves to ventricular venting graft patency and the postoperative ventriculogram. Our observations indicate that (1) Not all Q waves are due to occlusion of the saphenous bypass grafts (as noted by others.<sup>1, 16</sup>) (2) A certain percentage of new Q waves may not reflect true transmural myocardial infarction especially when all the vein grafts are patent and the postoperative ventriculograms show improvement (3) Some new Q waves reflect true transmural infarction due to occlusion of grafts or of distal coronary arteries with deteriorated left ventriculograms

(4) The high incidence of new Q waves in patients with ventricular vents is probably due to direct myocardial trauma at the apex of the left ventricle

### Material and methods

Between December 1970 and February 1976 720 patients underwent coronary bypass surgery at Long Island Jewish-Hillside Medical Center. Forty nine patients were excluded because they also underwent partial ventricular resection, prosthetic valve replacement or ventricular septal defect closure. Of the remaining 671 patients 56 patients developed new Q waves making up the case material for the present study. In 621 patients a saphenous vein graft was utilized for coronary bypass while in 50 patients the internal mammary artery was anastomosed to the left anterior descending artery.

All patients had preoperative left and right heart catheterization and left ventricular and selective coronary angiography using the Judkins<sup>5</sup> or the Sones and Shurey<sup>6</sup> techniques. In quantitating left ventricular dysfunction and the pattern of left ventricular contraction the same techniques and principles were used as previously reported,<sup>7</sup> utilizing the descriptive terminology suggested by Herman and associates.<sup>8</sup> Coronary arteries with at least 50 per cent reduction in diameter on coronary angiography were considered significantly stenosed and were bypassed whenever feasible. The severity and the extent of coronary disease was graded according to the criteria of Bruschke and associates.<sup>9</sup> Congestive

From the Department of Medicine, Cardiology Division and the Department of Surgery, Cardiothoracic Division, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. Queens Hospital Center, Affiliation, Jamaica, N.Y. and the School of Medicine, Health Sciences Center, State University of New York at Stony Brook, N.Y.

Received for publication Oct. 28, 1976.

Accepted for publication Dec. 1, 1976.

Reprint requests: Agop Aintablian, M.D., Cardiology Division, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040.

- with and without deafness in the same family *Am J Cardiol* 29 702 1972
- 10 Roy P R Emanuel R Ismail S A and El Tayeb M H Hereditary prolongation of the Q T interval genetic observation and management in three families with twelve affected members *Am J Cardiol* 37 237 1976
- 11 Schwartz P J, Periti M and Mailhans A The long Q T syndrome *Am Heart J* 89 378 1976
- 12 Yanowitz F Preston J B and Ahlstedt J A Functional distribution of right and left stellate innervation to the ventricles production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone *Circ Res* 18 416 1966
- 13 Moss A J and McDonald J Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long Q T interval syndrome *N Engl J Med* 285 903 1971
- 14 Schwartz P J and Mailhans A Electrical alternation of the T wave clinical and experimental evidence of its relationship with the sympathetic nervous system and the long Q T syndrome *Am Heart J* 89 45 1975
- 15 Olley P M and Fowler R S The surdo cardiac syndrome and therapeutic observations *Br Heart J* 32 467 1970
- 16 Leon D F Shaver J A and Leonard J J Reflex heart rate control in man *Am Heart J* 80 729 1970
- 17 Martin C E Shaver J A Leon D F Thompson M E Reddy P S and Leonard J J Autonomic mechanisms in hemodynamic responses to isometric exercise *J Clin Invest* 54 104 1974
- 18 Shaver J A Gorlin R and Paley H W Ganglionic blockade and left ventricular response to exercise (Abstr) *Fed Proc* 24 146 1965
- 19 Jose A D and Collison D The normal range and determinants of the intrinsic heart rate in man *Cardiovasc Res* 4 160 1970
- 20 Pernot C Henry M and Aigle J C Syndrome cardioauditif de Jervell et torsades de pointes *Arch Mal Coeur* 65 261 1972
- 21 Randall W C and Rohse W G The augmentor action of the sympathetic cardiac nerves *Circ Res* 4 77 1956
- 22 Mandel W J Hayakawa H Allen H N Danzig R, and Kermaier A J Assessment of sinus node function in patients with the sick sinus syndrome *Circulation* 46 761 1972
- 23 Jose A D and Taylor II R Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man *J Clin Invest* 48 2019 1969
- 24 Strauss H C Bigger J T Jr Saroff A L and Giardina M G V Electrophysiologic evaluation of sinus node function in patients with sinus node dysfunction *Circulation* 53 763 1976
- 25 Jose A D Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man *Am J Cardiol* 18 476 1966
- 26 Jose A D and Stitt F Effects of hypoxia and metabolic inhibitors on the intrinsic heart rate and myocardial contractility in dogs *Circ Res* 25 53 1969
- 27 James T N Congenital deafness and cardiac arrhythmias *Am J Cardiol* 19 627 1967
- 28 Green J R Korovetz M J Shanklin D R DeVito J J and Taylor W J Sudden unexpected death in three generations *Arch Intern Med* 124 304 1968
- 29 Vincent G M Ahlstedt J A Burgess M J and Miller K Autonomic manipulation in the inherited long Q T recurrent syncope syndrome (Abstr) *Am J Cardiol* 33 174 1974
- 30 Raizman R A Hunt D Russel R O Jr and Hackley C E QT interval prolongation paroxysmal ventricular arrhythmias and convulsive syncope *Ann Intern Med* 75 919 1971
- 31 Kolman B Verner R L and Lown B The effect of vagus nerve stimulation upon vulnerability of the canine ventricle role of sympathetic-parasympathetic interactions *Am J Cardiol* 37 1041 1978
- 32 Schwartz P J Snebold N G and Brown A M Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold *Am J Cardiol* 37 1034 1976

# Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. P O Box 765, Schenectady, N Y 12301 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works, or for resale.

# Significance of new Q waves after bypass grafting Correlations between graft patency, ventriculogram and surgical venting technique

Agop Aintablian MD  
Robert I Hamby MD  
Irwin Hoffman MD  
Daniel Weisz MD  
Choudary Voleti MD  
B George Wisoff MD

New Hyde Park Jamaica and Stony Brook N Y

New postoperative electrocardiographic Q waves have been described in eight to 40 per cent of patients undergoing bypass grafting for coronary artery disease.<sup>1-3</sup> Various theories have been proposed to explain these new Q waves.<sup>4</sup> Correlations of new Q waves to vein bypass occlusion, prolonged pump time or aortic cross clamping time are controversial.<sup>1-4</sup> Indeed whether or not the appearance of new postoperative Q waves means real transmural myocardial infarction is not clear. We report herein our experience with postoperative Q waves in 56 patients with vein bypass grafts and the relationship of new Q waves to ventricular venting graft patency and the postoperative ventriculogram. Our observations indicate that (1) Not all Q waves are due to occlusion of the saphenous bypass grafts (as noted by others).<sup>1-3</sup> (2) A certain percentage of new Q waves may not reflect true transmural myocardial infarction especially when all the vein grafts are patent and the postoperative ventriculograms show improvement. (3) Some new Q waves reflect true transmural infarction due to occlusion of grafts or of distal coronary arteries with deteriorated left ventriculograms.

(4) The high incidence of new Q waves in patients with ventricular vents is probably due to direct myocardial trauma at the apex of the left ventricle.

## Material and methods

Between December 1970 and February 1976 720 patients underwent coronary bypass surgery at Long Island Jewish-Hillside Medical Center. Forty nine patients were excluded because they also underwent partial ventricular resection, prosthetic valve replacement or ventricular septal defect closure. Of the remaining 671 patients 56 patients developed new Q waves making up the case material for the present study. In 621 patients, a saphenous vein graft was utilized for coronary bypass while in 50 patients the internal mammary artery was anastomosed to the left anterior descending artery.

All patients had preoperative left and right heart catheterization and left ventricular and selective coronary angiography using the Judkins<sup>5</sup> or the Sones and Shurey techniques. In quantitating left ventricular dysfunction and the pattern of left ventricular contraction, the same techniques and principles were used as previously reported,<sup>6</sup> utilizing the descriptive terminology suggested by Herman and associates.<sup>6</sup> Coronary arteries with at least 50 per cent reduction in diameter on coronary angiography were considered significantly stenosed and were bypassed whenever feasible. The severity and the extent of coronary disease was graded according to the criteria of Bruschke and associates.<sup>7</sup> Congestive

From the Department of Medicine, Cardiology Division and the Department of Surgery, Cardiothoracic Division, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y., Queens Hospital Center Affiliation, Jamaica, N.Y., and the School of Medicine, Health Sciences Center, State University of New York at Stony Brook, N.Y.

Received for publication Oct. 18, 1976.

Accepted for publication Dec. 17, 1976.

Reprint requests: Agop Aintablian, MD, Cardiology Division, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040.

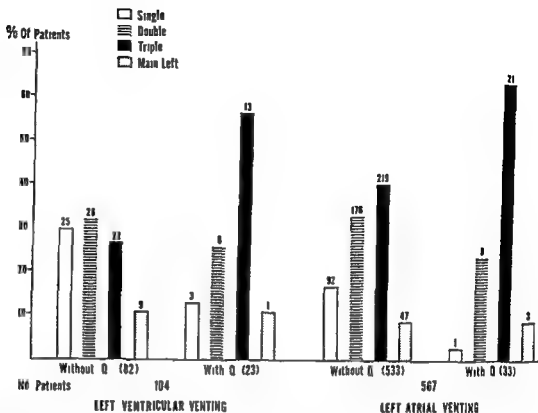


Fig 1 Comparison of the incidence of new Q waves in patients with ventricular or atrial venting revealed that patients with double or triple vessel disease had higher incidence of new Q waves as compared to those with single vessel disease

heart failure and cardiomegaly were defined according to the criteria we used in previous publication.<sup>22</sup> Post bypass recatheterization and angiography were done 10 to 15 days after surgery in order to assess the patency of the grafts, and any change in left ventricular function. Twelve lead electrocardiograms were performed on each patient on admission, on the day before surgery, then daily for the next four days and finally one day before discharge. All angiograms and electrocardiograms were reviewed by two different cardiologists in the comparison of pre and post operative studies. Electrocardiographic criteria used to evaluate the electrocardiogram were essentially Class I 1 and I 2 of the Minnesota code reported by Blackburn and associates.<sup>23</sup> Cases presenting transient ST segment or T wave changes but without pathologic Q waves were not included in the infarction pattern group. One hundred and forty two of the 671 patients were operated upon for preinfarction angina the same day of the cardiac catheterization as previously reported,<sup>24</sup> while 529 had elective surgery for angina.

Patients with saphenous vein bypasses to all coronary arteries with luminal narrowing greater than 50 per cent were considered complete revas-

cularizations while patients in whom saphenous vein bypasses could not be performed to one or more vessels with similar luminal narrowings were considered incomplete revascularizations.

#### Operative technique

All patients had reversed saphenous vein aorto coronary bypass utilizing total cardiopulmonary support. Priming solution was 5 per cent dextrose in one third normal saline. Flow rates were 40 to 55 ml/Kg using a bubble oxygenator with mean arterial pressures of at least 50 mm Hg. In 104 patients the left ventricle was vented through the apex and in the remaining 567 patients the left ventricle was vented through the right superior pulmonary vein. Moderate hypothermia was achieved by cooling the patient to 32° C. After total cardiopulmonary bypass the ventricle was occasionally electrically defibrillated and intermittently clamped for the distal anastomosis.

#### Results

**1 Effects of surgical venting technique on new Q wave incidence.** Of 671 operated on 104 (Group A) had intraoperative ventricular venting and 567 (Group B) had atrial venting. The inci-

dence of new Q waves in Group A was 23/104 (22 per cent) and in Group B 33/567 (5.8 per cent) ( $p < 0.05$ )

**2 Relation of the clinical profile and underlying coronary disease to the incidence of new Q waves** As seen in Table I comparison of age sex duration of angina coronary score history or location of prior myocardial infarction did not differ in patients with or without new Q waves. Also there was no difference in the incidence of normal or abnormal left ventricular segmental wall motion between the groups. Although there was a slightly higher incidence of cardiomegaly and congestive heart failure in patients who developed new Q waves the difference was not statistically significant. Main left coronary stenosis or unstable angina pectoris did not affect the incidence of new Q waves. Patients with double or triple vessel coronary disease had a higher incidence of new Q waves as compared to those with single vessel disease (Fig. 1).

**3 Relation of new Q waves to number of grafts placed** In the entire series of 671 operated patients 56 (8 per cent) had new postoperative Q waves. Of these 12 (6 per cent) occurred after single bypass in 207 patients, 24 (8 per cent) after double bypass in 287 patients, 18 (11 per cent) after triple bypass in 164 patients and two (15 per cent) after quadruple bypass in 13 patients. Thirty one new Q waves appeared on the anterior and septal walls, 23 on the inferior and infero-lateral walls and two on lateral walls (Table II).

**4 Relation of new Q waves to ungrafted vessels or to patent grafts with an occluded distal artery** New Q waves appeared in the zone of myocardium supplied by grafted arteries in all except three patients with ventricular venting (Cases No. 7 and 16) (Table III). In the latter three patients the Q waves occurred within zones of myocardium supplied by diseased but ungrafted vessels. In all the patients with new Q waves who were restudied only two (Cases 37 and 40) (with atrial venting and deteriorated left ventriculograms) demonstrated patent grafts but an occluded coronary artery beyond the distal anastomotic site (Table IV).

**5 Relation of new Q waves to postoperative alteration in left ventricular function and graft closure** In Group A (ventricular venting) 17 patients with new Q waves had postoperative

Table 1 Clinical profile

|   | Without new Q waves |     | With new Q waves |    |
|---|---------------------|-----|------------------|----|
|   | No.                 | %   | No.              | %  |
| Total number of patients                                | 615                 |     | 56               |    |
| Age (yrs.)  |                     |     |                  |    |
| Mean  | 54 ± 6              |     | 53 ± 11          |    |
| Range   | 28-84               |     | 37-76            |    |
| Sex   |                     |     |                  |    |
| Male  | 506                 | 82  | 49               | 87 |
| Female  | 109                 | 18  | 7                | 13 |
| Unstable angina   | 137                 | 21  | 10               | 18 |
| History of infarction                                   | 258                 | 42  | 24               | 43 |
| Documented ECG infarction                               |                     |     |                  |    |
| Septal  | 16                  | 9   | 2                | 7  |
| Anterior  | 38                  |     | 2                |    |
| Inferior  | 117                 | 19  | 12               | 20 |
| Inferior and anterior                                   | 21                  | 3   | 3                | 5  |
| Infero-dorsal, infero-lateral and dorsal                | 12                  | 2   | 3                | 5  |
| Normal QRS  | 411                 | 67  | 34               | 61 |
| Enlarged heart  | 45                  | 7   | 11               | 20 |
| Congestive heart failure                                | 25                  | 4   | 5                | 9  |
| Normal left ventricular contraction                     | 230                 | 37  | 24               | 43 |
| Segmental hypokinesia of one wall                       | 154                 | 25  | 13               | 23 |
| Akinesia of one wall                                    | 98                  | 16  | 9                | 16 |
| Akinesia or segmental hypokinesia of more than one wall | 103                 | 16  | 11               | 20 |
| Generalized hypokinesia                                 | 3                   | 0.5 | 0                | 0  |

ventriculograms. Of these (Table III) three (18 per cent) had an improved ventriculogram and 0/7 graft closures, 4 (24 per cent) had no change in the ventriculogram with 1/7 graft closure and in 10 patients (58 per cent) with deteriorated postoperative ventriculograms there were 7/16 graft closures (Table III). Of 17 patients in Group A who had postoperative ventriculograms five had single, 11 had double and one had triple bypass grafts.

In Group B (atrial venting) 25 patients with new Q waves were studied postoperatively. Of these (Table IV) five (20 per cent) had an improved ventriculogram and 0/11 graft closures. Fourteen (56 per cent) had an unchanged postoperative ventriculogram and 4/34 graft closures while six (24 per cent) had a deteriorated postoperative ventriculogram with 6/15 graft closures. Of these 25 patients four had single, eight had double, 12 had triple and one had quadruple



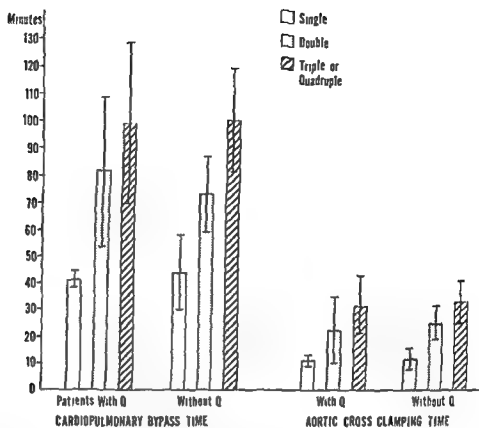


Fig 2 Comparison of over all cardiopulmonary bypass and aortic cross clamping time in patients with and without new Q waves did not show statistically significant difference

Table II Correlation of graft closure to the new Q waves and location of new Q waves in patients with ventricular and atrial venting

|                | Left ventricular venting |    | Left atrial venting |    | Total |    |
|----------------|--------------------------|----|---------------------|----|-------|----|
|                | No                       | %  | No                  | %  | No    | %  |
| Patients       | 23                       |    | 33                  |    | 56    |    |
| Grafts         | 42                       |    | 80                  |    | 122   |    |
| Pls studied    | 17                       | 74 | 25                  | 76 | 42    | 75 |
| Grafts closed  | 8/30                     | 27 | 9/60                | 15 | 17/90 | 19 |
| New Q waves    |                          |    |                     |    |       |    |
| Anterior       | 12                       | 52 | 12                  | 36 | 24    | 43 |
| Inferior       | 7                        | 31 | 14                  | 43 | 21    | 37 |
| Infero lateral | 2                        | 9  | 0                   | 0  | 2     | 4  |
| Septal         | 1                        | 4  | 6                   | 18 | 7     | 12 |
| Lateral        | 1                        | 4  | 1                   | 3  | 2     | 4  |

bypass grafts. Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5.8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in the ventricular vented group and 15 per cent in those with atrial venting.

6 Relation of the location of new Q waves to complete versus incomplete revascularization

and grafted vessels. All the new Q waves occurred within the zone of myocardium supplied by a grafted artery except for 3/56 (5 per cent) of the patients. These three new Q waves appeared in the inferior (Cases 6 and 7) or infero lateral (Case 16) wall in the group of patients with ventricular venting (Table III). Complete revascularization was performed in 50/104 (48 per cent) of the patients with ventricular venting in 369/567 (65 per cent) of those with atrial venting. Patients with ventricular venting and new Q waves had 13/23 (57 per cent) complete revascularization and those with atrial venting 21/33 (64 per cent), the difference was statistically insignificant indicating that completeness of revascularization did not affect the incidence of new Q waves.

7 Correlation of new Q waves to the duration of cardiopulmonary bypass aortic cross clamping time. In 350 patients with atrial venting there were no significant differences in the over all duration of cardiopulmonary bypass or aortic cross clamping time in those with or without new Q waves whether they had single or multiple vessel coronary bypass surgery (Fig 2). In patients with new Q waves the incidence of prolonged cardiopulmonary bypass time exceeding 100 minutes for double (30 per cent) and 120

Table III Correlation of location of new Q wave patency of graft and postoperative ventriculogram in Group A patients

| Patient          | Grafts |     |    | Patency |     |    | Contraction |                         | HY<br>MI | Admission<br>ECG Q wave | New Q                |
|------------------|--------|-----|----|---------|-----|----|-------------|-------------------------|----------|-------------------------|----------------------|
|                  | LAD    | RCA | CX | LAD     | RCA | CX | Preop       | Postop                  |          |                         |                      |
| LVG improved     |        |     |    |         |     |    |             |                         |          |                         |                      |
| 1                | X      | X   |    | +       | +   |    | As Ant      | Normal                  | 1        | Inferior                | Anterior             |
| 2                | X      | X   |    | +       | +   |    | As Ant      | Normal                  | 1        | RBBB +<br>Lateral       | Inferior             |
| 3                | X      | X   | X  | +       | +   | +  | As Ant      | Normal                  | 1        | Inferior<br>(narrow Q)  | Inferior<br>(wide Q) |
| LVG unchanged    |        |     |    |         |     |    |             |                         |          |                         |                      |
| 4                | X      |     | X  | +       |     | 0  | Normal      | Normal                  | 0        | Normal                  | Septal               |
|                  | X      |     |    | +       |     |    | Normal      | Normal                  | 0        | Inferior +<br>Lateral   | LAH +<br>Anterior    |
| 6                | X      |     | X  | +       |     | +  | Normal      | Normal                  | 0        | Normal                  | Inferior             |
| 7                | X      |     | X  | +       |     | +  | Normal      | Normal                  | 1        | T aV                    | Inferior             |
| LVG Deteriorated |        |     |    |         |     |    |             |                         |          |                         |                      |
| 8                | X      | X   |    | +       | +   |    | Ak Apic     | Ak Ant                  | 3        | T v                     | Anterior             |
| 9                | X      |     |    | 0       |     |    | Normal      | Ak Apic                 | 0        | Normal                  | Anterior             |
| 10               | X      | X   |    | 0       | 0   |    | As Apic     | Ak Ant                  | 0        | Inferior                | Anterior             |
| 11               | X      | X   |    | 0       | 0   |    | Normal      | Ak Apic                 | 2        | T v                     | Anterior             |
| 12               | X      |     |    | 0       |     |    | As Ant      | Ak Ant                  | 0        | LAH QRS<br>WNL          | Anterior             |
| 13               | X      | X   |    | +       | +   |    | Ak Ant      | As-Ant Ak<br>Inf + Apic | 3        | Anterior                | Inferior             |
| 14               | X      | X   |    | +       | +   |    | As-Inf      | Ak Inf                  | 3        | Normal                  | Inferior             |
| 15               |        | X   |    |         | +   |    | Normal      | Ak Apic                 | 0        | Normal                  | Inferior             |
| 16               | X      |     |    | 0       |     |    | Normal      | Ak Apic                 | 0        | Normal                  | Lateral              |
| 17               | X      | X   |    | +       | +   |    | As Inf      | Ak Inf<br>Ak Apic       | 2        | Normal                  | Inferolateral        |

Abbreviations: LAD = left anterior descending coronary artery RCA = right coronary artery CX = circumflex coronary artery Ak = Akinesis  
As = Segmental hypokinesis

minutes for triple or multiple bypass grafts (33 per cent) as compared to those with no Q waves (18 per cent and 13 per cent respectively) were slightly higher.

**8 Disappearance of Q waves** Two of our patients after coronary bypass surgery lost long standing anterior Q waves. Postoperative angiography in these two patients revealed patent saphenous bypass grafts and improved left ventriculogram in one while in the other the left ventriculogram was unchanged.

**9 Relation of mortality to graft patency** Twelve patients died within one month after bypass surgery (Table V). Three patients died in the operating room. One of them (Case 2) probably had a myocardial infarction the morning of surgery. Of nine patients who died within two weeks after surgery, two died of non cardiac causes, one died of combined cardiac and

non cardiac causes whereas six patients' deaths were secondary to myocardial infarction. The mortality in two patients who died after discharge at home was due to myocardial infarction in one (Case 10) and in the other due to myocardial infarction or ventricular arrhythmia (Case 11). It should be mentioned that 2/12 (17 per cent) who died had balloon assist prior to surgery for persistent angina or cardiogenic shock (Cases 6 and 11) and one patient was brought to the operating room after arrest while external cardiac massage was being performed (Case 1). Of 12 patients who died, three (25 per cent) had main left coronary stenosis.

#### Discussion

An 8 per cent incidence of new Q waves in our series is lower than reported by others.<sup>11,12</sup> Contrary to the report of Williams and asso

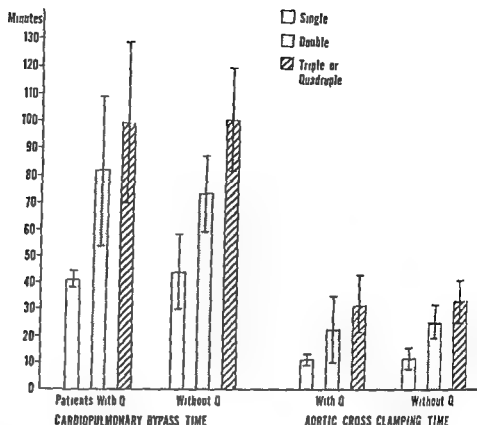


Fig 2 Comparison of over all cardiopulmonary bypass and aortic cross clamping time in patients with and without new Q waves did not show statistically significant difference

Table II Correlation of graft closure to the new Q waves and location of new Q waves in patients with ventricular and atrial venting

|                | Left ventricular venting |    | Left atrial venting |    | Total |    |
|----------------|--------------------------|----|---------------------|----|-------|----|
|                | No                       | %  | No                  | %  | No    | %  |
| Patients       | 23                       |    | 33                  |    | 56    |    |
| Grafts         | 42                       |    | 80                  |    | 122   |    |
| Pts studied    | 17                       | 74 | 25                  | 76 | 42    | 75 |
| Grafts closed  | 8/30                     | 27 | 9/60                | 15 | 17/90 | 19 |
| New Q waves    |                          |    |                     |    |       |    |
| Anterior       | 12                       | 52 | 12                  | 36 | 24    | 43 |
| Inferior       | 7                        | 31 | 14                  | 43 | 21    | 37 |
| Infero lateral | 2                        | 8  | 0                   | 0  | 2     | 4  |
| Septal         | 1                        | 4  | 6                   | 18 | 7     | 12 |
| Lateral        | 1                        | 4  | 1                   | 3  | 2     | 4  |

bypass grafts. Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5.8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in the ventricular vented group and 15 per cent in those with atrial venting.

**B** Relation of the location of new Q waves to complete versus incomplete revascularization

and grafted vessels. All the new Q waves occurred within the zone of myocardium supplied by a grafted artery except for 3/56 (5 per cent) of the patients. These three new Q waves appeared in the inferior (Cases 3 and 7) or infero lateral (Case 16) wall in the group of patients with ventricular venting (Table III). Complete revascularization was performed in 50/104 (48 per cent) of the patients with ventricular venting in 369/567 (65 per cent) of those with atrial venting. Patients with ventricular venting and new Q waves had 13/23 (57 per cent) complete revascularization, and those with atrial venting 21/33 (64 per cent), the difference was statistically insignificant indicating that completeness of revascularization did not affect the incidence of new Q waves.

**7** Correlation of new Q waves to the duration of cardiopulmonary bypass, aortic cross clamping time. In 350 patients with atrial venting there were no significant differences in the over all duration of cardiopulmonary bypass or aortic cross clamping time in those with or without new Q waves whether they had single or multiple vessel coronary bypass surgery (Fig 2). In patients with new Q waves the incidence of prolonged cardiopulmonary bypass time exceeding 100 minutes for double (30 per cent) and 120

mortality rate of only 6 per cent (3/50) (Cases 4 6 8 Table V) in the patients developing post bypass new Q waves was much lower than reported mortality rate in CCUs by different centers namely 9.8 per cent to 23 per cent.<sup>17</sup> This suggests that new post bypass Q waves may not represent true transmural myocardial infarctions. Most of the patients with sudden development of postoperative new Q waves had a benign hospital course and were not clinically different from patients without new Q waves. This has also been noted by others.<sup>18</sup> Patients with presumed true myocardial infarction not only had elevated SGOT and other enzyme levels but their electrocardiograms demonstrated evolutionary changes of transmural myocardial infarction usually localized on the anterior wall of the left ventricle. Although Fruehan and associates<sup>19</sup> noted that 74 per cent (28/38) of new Q waves were located in the inferior dorsal or infero lateral wall in their series of 199 patients we encountered new Q waves in those locations in only 41 per cent (23/56).

Three of 56 patients with new Q waves and a history of previous myocardial infarction (Cases 3 20 36 Tables III and IV) developed significant Q waves in the inferior or anterior wall sites of previous narrow Q waves. These electrocardiographic changes which suggest unmasking of an old myocardial infarction pattern may also be due to a localized conduction disturbance in an area of previous infarction due to redistribution of electrical forces after bypass surgery or to a change of axis secondary to surgery. The left ventriculograms in these patients improved or did not change after the appearance of significant new Q waves. However none of our patients after coronary bypass surgery manifested the phenomenon of unmasking of old infarction described by Bassan and associates.<sup>20</sup> It is worth mentioning that two of our patients after coronary bypass surgery and patent grafts lost long standing anterior Q waves which also has been observed by Conde and associates.<sup>21</sup>

A striking decrease in the incidence of postoperative Q waves (from 22 per cent to 5.8 per cent) occurred when atrial rather than ventricular venting was adopted. This result may be due in part to improved surgical bypass techniques since the ventricular vented cases were done at the start of the coronary bypass surgery program in our institution. The over all incidence of saph-

nous bypass graft closure was higher in the early operated group. In the ventricular venting group the graft closure rate was 22 per cent versus 8 per cent in those patients with atrial venting. In patients with new Q waves and ventricular venting who had a postoperative study (Table II) the graft closure rate was twice as high as compared to the atrial venting group (27 per cent versus 15 per cent). However the incidence of the new Q waves was much higher in the ventricular venting group (22 per cent) as compared at atrial venting patients (5.8 per cent). Thus improved surgical techniques and fewer graft closures alone cannot explain such a drop in the incidence of new Q waves. The clear implication is that sufficient myocardial trauma results from ventricular venting to result in pathologic Q waves. The anatomic placement of ventricular vents at or near the apex could account for either inferior or anterior wall localization of the postoperative Q waves. Since the ventricular trauma produced by venting is not due to arterial occlusion there is no wide surrounding ischemic area. Thus it is not surprising that postoperative Q waves attributable to venting are not usually associated with impaired ventricular function in the absence of graft occlusion. Indeed improved ventricular function may be observed. However in four patients (Cases 13 14 15 and 17) in whom new inferior Q waves developed new dysfunction of the inferior wall and open grafts to the right coronary artery could be demonstrated. Here we assume that the deterioration in the ventriculogram was probably secondary to the trauma of venting. In contrast are Cases 7 9 10 11 12 16 19 38 and 39 all of whom developed new anterior Q waves and anterior wall dysfunction in the presence of occluded grafts to the left anterior descending artery or its diagonal branch. Here the assumption must be that true infarction secondary to inadequate arterial and graft inflow occurred.

The incidence of new Q waves was higher in patients with double triple or quadruple bypass surgery as compared to those with a single bypass as reported by others. Although our patients with atrial venting had a higher percentage of complete revascularizations the incidence of new Q waves was not affected by complete or incomplete revascularization in patients in either the atrial or ventricular venting groups. All of the new Q waves occurred within

Table IV Correlation of location of new Q wave patency of graft, and postoperative ventriculogram in Group B patients

| Patient          | Grafts |     |    | Patency |     |    | Contraction        |                    | Hx<br>MI                               | Admission<br>ECG Q wave                      | New Q              |
|------------------|--------|-----|----|---------|-----|----|--------------------|--------------------|--|--|--------------------|
|                  | LAD    | RCA | CA | LAD     | RCA | CA | Preop              | Postop             |  |  |                    |
| LVG improved     |        |     |    |         |     |    |                    |                    |  |  |                    |
| 18               | X      | X   | λ  | +       | +   | +  | As Ant<br>Apic     | Normal             | 0                                      | T <sub>1</sub> ,                             | Septal             |
| 19               | X†     |     |    | +       |     |    | As Apic            | Normal             | 0                                      | Normal                                       | Septal             |
| 20               | λ      | λ   |    | +       | +   |    | Ak Ant<br>Apic     | As Ant<br>Apic + 1 | Small Q with good<br>RV V <sub>1</sub> |  | Q <sub>1</sub> λ , |
| 21               | X      | λ   |    | +       | +   |    | Ak Inf<br>Ant      | Normal             | 0                                      | TV <sub>1</sub> V <sub>1</sub>               | Inferior           |
| 22               | X      | λ   | λ  | +       | +   | +  | Ak Ant<br>Apic     | Normal             | 0                                      | Normal                                       | Inferior           |
| LVG unchanged    |        |     |    |         |     |    |                    |                    |  |  |                    |
| 23               | λ      | X   | λ  | +       | 0   | +  | As Apic            | As Apic            | 1                                      | Normal                                       | Septal             |
| 24               | λ      |     | λ  | +       |     | +  | Ak Inf             | Ak Inf             | 1                                      | Inferior                                     | Anterior           |
| 25               | X†     |     |    | +       |     |    | As Ant             | As Ant             | 2                                      | Infero dorso<br>lateral                      | Anterior           |
| 26               | X      | X   | X  | +       | +   | 0  | Ak Inf             | Ak Inf             | 0                                      | Normal                                       | Anterior           |
| 27               | X      | X   | λ  | +       | +   | 0  | Ak Apic            | Ak Apic            | 0                                      | Normal                                       | Inferior           |
| 28               | λ      | λ   |    | +       | +   |    | Normal             | Normal             | 1                                      | TV <sub>1</sub> V <sub>1</sub>               | Inferior           |
| 29               | X      | X   | X  | +       | +   | +  | Normal             | Normal             | 0                                      | T <sub>1</sub> , aV <sub>r</sub>             | Inferior           |
| 30               | X      | X   |    | +       | +   |    | Normal             | Normal             | 0                                      | Normal                                       | Inferior           |
| 31               | λ      | λ   | λ  | +       | +   | +  | Normal             | Normal             | 0                                      | Normal                                       | Inferior           |
| 32               | X      | X   |    | 0       |     |    | Ak Inf             | Ak Inf             | 0                                      | T <sub>1</sub> ,                             | Inferior           |
| 33               | X      | X   | X  | +       | +   | +  | Normal             | Normal             | 0                                      | Normal                                       | Inferior           |
| 34               | X      | X   | X  | +       | +   | +  | Normal             | Normal             | 0                                      | T <sub>1</sub> aV <sub>r</sub>               | Inferior           |
| 35               | X†     | X   | X  | +       | +   | 0  | Normal             | Normal             | 1                                      | Normal                                       | Inferior           |
| 36               |        | X   | λ  | +       | +   | +  | Normal             | Normal             | 2                                      | Anterior + small<br>Q II III aV <sub>r</sub> | Inferior           |
| LVG deteriorated |        |     |    |         |     |    |                    |                    |  |  |                    |
| 37               | X      |     |    | +       | *   |    | Normal             | Ak Apic            | 0                                      | Normal                                       | Septal             |
| 38               | 0      |     | λ  | 0       |     | +  | As Ant<br>Ak Basal | Ak Ant<br>Ak Basal | 1                                      | Q II III aV <sub>r</sub>                     | Anterior           |
| 39               | X      | X   | λ  | 0       | 0   | 0  | As Ant             | Ak Ant<br>Inf      | 1                                      | Inferior + lateral                           | Anterior           |
| 40               | λ      | λ   | X  | +       | +   | +  | Normal             | Ak Ant<br>Apic     | 0                                      | Normal                                       | Anterior           |
| 41               | X      |     | λ  | 0       |     | +  | As Ant<br>Apic     | Ak Apic            | 0                                      | T <sub>1</sub> ,                             | Lateral            |
| 42               | λ†     | X   | X  | +       | +   | 0  | Normal             | Ak Inf             | 0                                      | T <sub>1</sub> ,                             | Inferior           |

Abbreviations as in Table III

† Patent graft but occluded distal left anterior descending artery (cases 37 and 40)

‡ Internal mammary anastomosis to left anterior descending artery

ciates' main left coronary stenosis did not increase the incidence of new Q waves. The age, sex, duration of disease, preinfarction angina, previous myocardial infarction or abnormal left ventricular wall motion did not affect the incidence of new Q waves. Patients with double or triple vessel disease as well as those with cardiomegaly or congestive heart failure had a higher incidence of new Q waves, but this differ-

ence was not statistically significant. Of 12 patients who died after coronary bypass surgery, eight died (Table V) of definite acute myocardial infarction, one probably of acute myocardial infarction or ventricular tachyarrhythmia (Case 11, Table V), two of massive pulmonary embolism and one after an extensive cerebrovascular accident. Of these 12 patients, 25 per cent had significant main left coronary artery disease. The

# Comments

After cardiac catheterization had chest pain then arrested. With external cardiac massage was brought to OR and double bypass done. Died 4 days later. Autopsy showed patent grafts with recent anterior infarction. The morning of surgery had protracted chest pain with ST elevation. Autopsy showed fresh anterior infarction. Died 24 hours postop. No autopsy.

Postoperative stormy course. No autopsy. Autopsy showed pulmonary embolism with patent grafts. Balloon assist + nitroprusside for persistent angina. Postop developed anterior Q wave then LBBB before death. No autopsy. Developed LBBB + LPH before death. No autopsy.

Expired 3 wks. postop. Autopsy showed fresh anterior infarct and closure of graft. Balloon assisted angiogram done. Discharged home after triple patent grafts. Died in his sleep. Protracted pleuritic pain. Had persistent pericardial rub. Autopsy showed bilateral massive pulmonary emboli + fresh anterior infarct and patent grafts.

per cent of left ventriculograms deteriorated while 43 per cent were unchanged and 19 per cent improved after surgery. Indeed in the patients without new Q waves 9 per cent (77/880) of grafts were closed indicating that graft occlusion can occur without necessarily causing electrocardiographic changes of transmural myocardial infarction. It is important to note that in our series patients with single bypass grafts in whom the postoperative left ventriculogram showed deterioration invariably had an occluded bypass graft or a patent graft with occlusion of the coronary artery distal to the anastomosis (Tables III and IV). At least four or five patients developed severe hypotension prior to bypass surgery. These patients most likely sustained myocardial infarction at that moment and electrocardiographic changes of transmural myocardial infarction appeared after completion of the bypass due to reperfusion of the infarcted area since bypass grafts studied postoperatively were patent in this group. The delayed appearance of new Q waves

after coronary occlusion in dogs has been explained by Blumenthal and associates.<sup>11</sup> Possible preservation of the sarcolemmal membranes delays the appearance of Q waves in the early phase of infarction but after reperfusion disruption of these membranes accelerates the emergence of Q waves.

When new Q waves appeared after bypass using the atrial venting technique with ventricular function unimproved or worsened graft closure or occlusion of the distal coronary artery was common. A compromised arterial inflow and true myocardial infarction must be presumed.

Of great interest are those patients with new Q waves following atrial venting with improved ventriculograms and patent grafts. The new Q waves must be a consequence of surgical trauma since aortic cross clamp and cardiopulmonary bypass times were not significantly prolonged. Two possibilities are suggested. First direct myocardial damage with muscle necrosis may occur sufficient to produce Q waves but nevertheless undetectable by ventriculography. Second the surgical trauma might result in localized ventricular conduction delays or blocks affecting the early QRS balance as postulated by Castellanos and Lemberg.<sup>12</sup> They theorized that such local delays in ischemic tissue result in slurring or widening of the QRS producing 'infarct Qs'. It seems reasonable that a similar mechanism in traumatized tissue may account for postoperative Q waves in these patients with improved ventriculograms and patent grafts.

Clinical significance and prognosis. Postbypass grafting Q waves as described and discussed have a varied pathogenesis. When accompanied by improvement in ventricular function and patent grafts they are of little significance and do not carry the prognostic importance of myocardial infarction as it occurs in the natural course of arteriosclerotic heart disease. In contrast when accompanied by graft closure and deteriorated ventricular function the mechanism may be presumed ischemic and the prognosis must take into account the likelihood of permanent or long term localized ventricular dysfunction.

## Summary

New Q waves were observed in 56 (8 per cent) of 671 patients undergoing saphenous vein bypass

Table V Circumstances and causes of death

| Patient no | No of diseased vessels | Old myocardial infarction | Died  |              |                | New Q waves             | Causes of death |                    |                          |
|------------|------------------------|---------------------------|-------|--------------|----------------|-------------------------|-----------------|--------------------|--------------------------|
|            |                        |                           | In OR | Within 2 wks | Within 1 month |                         | Infarction      | Pulmonary embolism | Cerebrovascular accident |
| LV VENT    |                        |                           |       |              |                |                         |                 |                    |                          |
| 1          | 3                      | Inferior                  | -     | +            | -              | Anterior                | +               | -                  | -                        |
| 2          | M 3                    | Inferior                  | +     | -            | -              | -                       | +               | -                  | -                        |
| 3          | 2                      | Inferior                  | -     | +            | -              | -                       | -               | -                  | +                        |
| LA VENT    |                        |                           |       |              |                |                         |                 |                    |                          |
| 4          | 3                      | 0                         | -     | +            | -              | Inferior + LPH + RBBB   | +               | -                  | -                        |
| 5          | 2                      | Anterior + LAH            | -     | +            | -              | -                       | -               | +                  | -                        |
| 6          | 3                      | Inferior                  | -     | +            | -              | Anterior                | +               | -                  | -                        |
| 7          | 3                      | 0                         | +     | -            | -              | -                       | +               | -                  | -                        |
| 8          | 3                      | Anterior + Inferior       | -     | +            | -              | Anterior                | +               | -                  | -                        |
| 9          | M 2                    | 0                         | +     | -            | -              | -                       | +               | -                  | -                        |
| 10         | 1                      | 0                         | -     | -            | +              | Anterior (3 wks postop) | +               | -                  | -                        |
| 11         | 3                      | Anterior + inferior       | -     | -            | +              | -                       | Probable        | -                  | -                        |
| 12         | M 3                    | 0                         | -     | +            | -              | -                       | +               | +                  | -                        |

Abbreviations: M = main left coronary artery; LAH = left anterior hemiblock; LPH = left posterior hemiblock; RBBB = right bundle branch block.

the zone of myocardium supplied by the grafted artery except three (5 per cent) of the patients in the ventricular vented group in whom the new Q wave appeared in non-grafted vessel zones of inferior or infero lateral wall. This result is different from the report of Assad Morell and colleagues<sup>11</sup> in which 25 per cent of the patients manifested new Q waves in a zone of myocardium supplied by a diseased ungrafted artery. It is worth mentioning that in three patients with atrial venting and with patent saphenous vein bypass grafts the coronary artery distal to the anastomosis was closed. This explains the appearance of their new Q waves as well as the observed deterioration of left ventricular contractility.

Although Anderson and associates<sup>3</sup> noted no direct correlation between ECG evidence of transmural myocardial infarction and graft closure they did not comment on the corresponding ventriculography. Brewer and associates<sup>16</sup> confirmed these findings in autopsy studies of

patients dying after coronary bypass surgery. In the present study new Q waves were noted in patients with deteriorated, unchanged or even improved ventriculograms. When the data on new Q waves and postoperative ventricular function were correlated no direct relationship could be seen. However, when graft patency was also considered, a clear relationship emerged. Improved postoperative ventricular function correlated well with graft patency, despite Q waves. Unimproved or deteriorated ventricular function did not predict graft occlusion since more than half of the vein grafts placed in these patients were patent. Assad Morell and associates<sup>11</sup> also noted a lack of correlation between graft closure and electrocardiographic and angiographic evidence of myocardial infarction. Half their 32 patients had patent grafts despite evidence of myocardial infarction in the area of distribution of the grafted vessels.

In our series only 19 per cent of grafts were closed in patients with new Q waves and only 38

# Comments

After cardiac catheterization had chest pain then arrested  
With external cardiac massage was brought to B R and  
double bypass done Died 4 days later Autopsy showed  
patent grafts with recent anterior infarction  
The morning of surgery had protracted chest pain with ST  
elevation Autopsy showed fresh anterior infarction  
Died 24 hours postop No autopsy

Postoperative stormy course No autopsy  
Autopsy showed pulmonary embolism with patent grafts  
Balloon assist + nitroprusside for persistent angina Postop  
developed anterior Q wave then LBBB before death  
No autopsy  
Developed LBBB + LPH before death  
No autopsy

Expired 3 wks postop Autopsy showed fresh anterior  
infarct and closure of graft  
Balloon assisted angiograms done Discharged home after  
triple patent grafts Died in his sleep  
Protracted pleuritic pain Had persistent pericardial rub  
Autopsy showed bilateral massive pulmonary emboli +  
fresh anterior infarct and patent grafts

per cent of left ventriculograms deteriorated while 43 per cent were unchanged and 19 per cent improved after surgery Indeed in the patients without new Q waves 11 per cent (77/885) of grafts were closed indicating that graft occlusion can occur without necessarily causing electrocardiographic changes of transmural myocardial infarction It is important to note that in our series patients with single bypass grafts in whom the postoperative left ventriculogram showed deterioration invariably had an occluded bypass graft or a patent graft with occlusion of the coronary artery distal to the anastomosis (Tables III and IV) At least four or five patients developed severe hypotension prior to bypass surgery These patients most likely sustained myocardial infarction at that moment and electrocardiographic changes of transmural myocardial infarction appeared after completion of the bypass due to reperfusion of the infarcted area since bypass grafts studied postoperatively were patent in this group The delayed appearance of new Q waves

after coronary occlusion in dogs has been explained by Blumenthal and associates<sup>21</sup> Possible preservation of the sarcolemmal membranes delays the appearance of Q waves in the early phase of infarction but after reperfusion, disruption of these membranes accelerates the emergence of Q waves

When new Q waves appeared after bypass using the atrial venting technique with ventricular function unimproved or worsened graft closure or occlusion of the distal coronary artery was common A compromised arterial inflow and true myocardial infarction must be presumed

Of great interest are those patients with new Q waves following atrial venting with improved ventriculograms and patent grafts The new Q waves must be a consequence of surgical trauma since aortic cross clamp and cardiopulmonary bypass times were not significantly prolonged Two possibilities are suggested First direct myocardial damage with muscle necrosis may occur sufficient to produce Q waves but nevertheless undetectable by ventriculography Second the surgical trauma might result in localized ventricular conduction delays or blocks affecting the early QRS balance as postulated by Castellanos and Lemberg<sup>22</sup> They theorized that such local delays in ischemic tissue result in slurring or widening of the QRS producing infarct Qs It seems reasonable that a similar mechanism in traumatized tissue may account for postoperative Q waves in these patients with improved ventriculograms and patent grafts

Clinical significance and prognosis Postbypass grafting Q waves as described and discussed have a varied pathogenesis When accompanied by improvement in ventricular function and patent grafts they are of little significance and do not carry the prognostic importance of myocardial infarction as it occurs in the natural course of arteriosclerotic heart disease In contrast when accompanied by graft closure and deteriorated ventricular function the mechanism may be presumed ischemic and the prognosis must take into account the likelihood of permanent or long term localized ventricular dysfunction

## Summary

New Q waves were observed in 56 (8 per cent) of 671 patients undergoing saphenous vein bypass



Table V Circumstances and causes of death

| Patient no | No of diseased vessels | Old myocardial infarction | Died  |              |                | New Q waves             | Causes of death |                    |                         |
|------------|------------------------|---------------------------|-------|--------------|----------------|-------------------------|-----------------|--------------------|-------------------------|
|            |                        |                           | In OR | Within 2 wks | Within 1 month |                         | Infarction      | Pulmonary embolism | Coronary artery disease |
| LV VENT    |                        |                           |       |              |                |                         |                 |                    |                         |
| 1          | 3                      | Inferior                  | -     | +            | -              | Anterior                | +               | -                  | -                       |
| 2          | M                      | Inferior                  | +     | -            | -              | -                       | -               | -                  | -                       |
| 3          | 3                      | Inferior                  | -     | +            | -              | -                       | +               | -                  | -                       |
| LA VENT    |                        |                           |       |              |                |                         |                 |                    |                         |
| 4          | 3                      | 0                         | -     | +            | -              | Inferior + LPH + RBBB   | +               | -                  | +                       |
| 5          | 2                      | Anterior + LAH            | -     | +            | -              | -                       | +               | -                  | -                       |
| 6          | 3                      | Inferior                  | -     | +            | -              | Anterior                | +               | +                  | -                       |
| 7          | 3                      | 0                         | +     | -            | -              | -                       | +               | -                  | -                       |
| 8          | 3                      | Anterior + Inferior       | -     | +            | -              | Anterior                | +               | -                  | -                       |
| 9          | M                      | 0                         | +     | -            | -              | -                       | +               | -                  | -                       |
| 10         | 2                      |                           |       |              |                |                         | +               | -                  | -                       |
| 11         | 1                      | 0                         | -     | -            | +              | Anterior (3 wks postop) | +               | -                  | -                       |
| 12         | 3                      | Anterior + inferior       | -     | -            | +              | -                       | Probable        | -                  | -                       |
|            | M                      | 0                         | -     | +            | -              | -                       | +               | +                  | -                       |
|            | 3                      |                           |       |              |                |                         |                 |                    |                         |

Abbreviations M = main left coronary artery LAH = left anterior hemiblock LPH = left posterior hemiblock RBBB = right bundle branch block

the zone of myocardium supplied by the grafted artery, except three (5 per cent) of the patients in the ventricular vented group in whom the new Q wave appeared in non grafted vessel zones of inferior or infero lateral wall. This result is different from the report of Assad Morell and colleagues,<sup>11</sup> in which 25 per cent of the patients manifested new Q waves in a zone of myocardium supplied by a diseased ungrafted artery. It is worth mentioning that in three patients with atrial venting and with patent saphenous vein bypass grafts the coronary artery distal to the anastomosis was closed. This explains the appearance of their new Q waves as well as the observed deterioration of left ventricular contractility.

Although Anderson and associates<sup>7</sup> noted no direct correlation between FCG evidence of transmural myocardial infarction and graft closure they did not comment on the corresponding ventriculography. Brewer and associates<sup>16</sup> confirmed these findings in autopsy studies of

patients dying after coronary bypass surgery. In the present study, new Q waves were noted in patients with deteriorated, unchanged or even improved ventriculograms. When the data on new Q waves and postoperative ventricular function were correlated no direct relationship could be seen. However when graft patency was also considered, a clear relationship emerged. Improved postoperative ventricular function correlated well with graft patency, despite Q waves. Unimproved or deteriorated ventricular function did not predict graft occlusion, since more than half of the vein grafts placed in these patients were patent. Assad Morell and associates<sup>11</sup> also noted a lack of correlation between graft closure and electrocardiographic and angiographic evidence of myocardial infarction. Half their 32 patients had patent grafts, despite evidence of myocardial infarction in the area of distribution of the grafted vessels.

In our series only 19 per cent of grafts were closed in patients with new Q waves and only 38

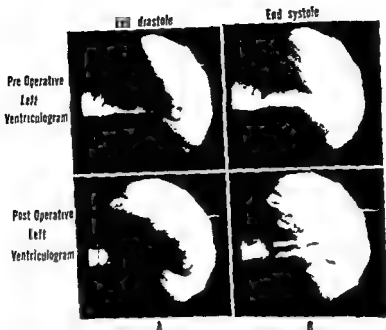


Fig 5 Pre and postoperative left ventriculograms of a patient with atrial venting and new anterior Q waves (Case No 37) Postoperatively the vein graft was patent with occluded distal left anterior descending artery and new hypokinesia of the apical segment of the left ventricle (arrow)

of angina previous myocardial infarction or main left coronary lesions did not affect the incidence of new Q waves. Although new Q waves were more frequent in patients with preoperative cardiomegaly and congestive heart failure this difference was not statistically significant. However there was no significant difference in the over all cardiopulmonary bypass or aortic cross clamping time in patients with or without new Q waves. Cardiopulmonary bypass time exceeding 100 minutes in patients with double bypasses and more than 120 minutes with multiple bypasses were more frequent in patients with new Q waves. Completeness or incompleteness of the revascularization procedure did not affect the incidence of new Q waves. In all but three patients with ventricular venting new Q waves appeared in a zone of myocardium supplied by a grafted artery. In the three exceptions the Q waves occurred within the zone of myocardium supplied by diseased but ungrafted vessels. In the ventricular vented group 7 (41 per cent) demonstrated an improved or unchanged postoperative ventriculogram with 7 per cent graft closure and 10 (59 per cent) had deteriorated ventriculograms with 44 per cent graft closure. In 25 patients with atrial venting 19 (76 per cent) showed improved or unchanged postoperative ventriculogram with 12 per cent graft closure and 6 (14 per cent) had

deteriorated ventriculograms with 40 per cent graft closure. Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5.8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in ventricular vented group and 15 per cent in those with atrial venting.

These findings indicate a poor correlation between new Q waves and graft closure. Improved postoperative ventriculograms correlated well with graft patency despite new Q waves. The etiology of new post bypass graft Q waves are varied. They include direct ventricular trauma and conduction delays resulting from surgery or venting as well as true ischemic infarction. Infarction may be due to compromised arterial inflow either in non operated diseased vessels in vessels distal to anastomoses with patent grafts or due to graft closure.

#### REFERENCES

1. Williams D, Iben A, Jurley E, Miller H, Bonanno J, Massimo R, Zeis R, Mason D T and Amsterdam E A. Myocardial infarction during coronary artery bypass surgery (Abstr.) *Am J Cardiol* 31:164 1973.
2. Fredberg D, Zeff H, Siberman R., et al. Myocardial infarction following coronary surgery. Vectorcardiographic assessment (Abstr.) *Am J Cardiol* 31:137 1973.
3. Anderson W T, Brundage B H and Chestlin, M D.

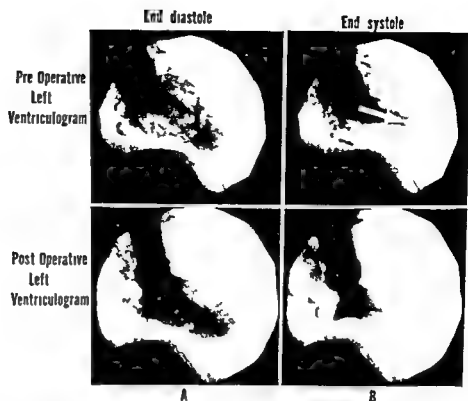


Fig 3 Pre and postoperative angiographic study of a patient with atrial venting who after triple vein bypass surgery developed new septal Q waves (Case No 18) As seen here segmental hypokinesia of the anteroapical segment of the left ventricle (arrow) was no more present in the postoperative left ventriculogram

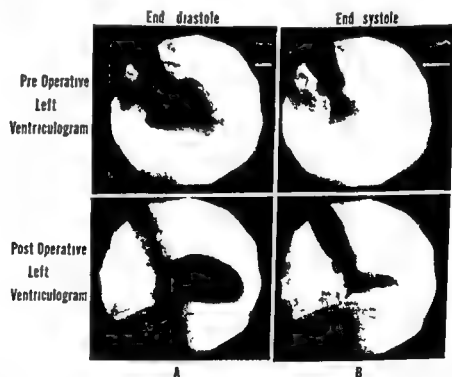


Fig 4 Comparison of pre and postoperative left ventricular contractile pattern of Case No 27 Left ventriculogram did not show any significant change although postop he developed new inferior Q waves

grafting with an over all mortality rate of 1.8 per cent. Forty two of the 56 (75 per cent) had postoperative ventriculograms and arteriograms and are reported herein. Ventricular venting was used intraoperatively in 17 patients and atrial venting in 25. Thirty one patients had new ante-

rior and/or septal Q waves while 23 had inferior or infero lateral and 2 had lateral Q waves. The incidence of new Q waves in patients with ventricular venting was 22 per cent and in those with atrial venting it was 5.8 per cent ( $p < 0.05$ ). Age, sex, duration of disease, severity

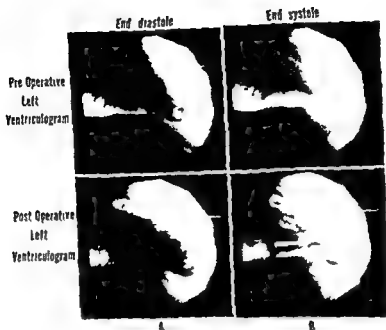


Fig 5 Pre- and postoperative left ventriculograms of a patient with atrial venting and new anterior Q waves (Case No 37). Postoperatively the vein graft was patent with occluded distal left anterior descending artery and new hypokinesia of the apical segment of the left ventricle (arrow.)

of angina previous myocardial infarction or main left coronary lesions did not affect the incidence of new Q waves. Although new Q waves were more frequent in patients with preoperative cardiomegaly and congestive heart failure this difference was not statistically significant. However there was no significant difference in the over all cardiopulmonary bypass or aortic cross clamping time in patients with or without new Q waves. Cardiopulmonary bypass time exceeding 100 minutes in patients with double bypasses and more than 120 minutes with multiple bypasses were more frequent in patients with new Q waves. Completeness or incompleteness of the revascularization procedure did not affect the incidence of new Q waves. In all but three patients with ventricular venting new Q waves appeared in a zone of myocardium supplied by a grafted artery. In the three exceptions the Q waves occurred within the zone of myocardium supplied by diseased but ungrafted vessels. In the ventricular vented group 7 (41 per cent) demonstrated an improved or unchanged postoperative ventriculogram with 7 per cent graft closure and 10 (59 per cent) had deteriorated ventriculograms with 44 per cent graft closure. In 25 patients with atrial venting 19 (76 per cent) showed improved or unchanged postoperative ventriculogram with 12 per cent graft closure and 6 (14 per cent) had

deteriorated ventriculograms with 40 per cent graft closure. Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5.8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in ventricular vented group and 15 per cent in those with atrial venting.

These findings indicate a poor correlation between new Q waves and graft closure. Improved postoperative ventriculograms correlated well with graft patency despite new Q waves. The etiology of new post bypass graft Q waves are varied. They include direct ventricular trauma and conduction delays resulting from surgery or venting as well as true ischemic infarction. Infarction may be due to compromised arterial inflow either in non operated diseased vessels in vessels distal to anastomoses with patent grafts or due to graft closure.

#### REFERENCES

1. Williams D, Iben A, Jurley E, Miller R, Bonanno J, Masumi, R, Zelis H, Mason III T and Amsterdam E. A. Myocardial infarction during coronary artery bypass surgery (Abstr.) *Am J Cardiol* 31:164 1973.
2. Friedberg D, Zelt H, Sberman R et al. Myocardial infarction following coronary surgery. Vectorcardiographic assessment (Abstr.) *Am J Cardiol* 31:132 1973.
3. Anderson W T, Brundage B H and Chestlin M D

- Vectorcardiographic changes following coronary artery bypass surgery *Am Heart J* 87 421 1974
- 4 Espinoza J Lipski J Litwak R Donoso E and Kack S New Q waves after coronary artery bypass surgery for angina pectoris *Am J Cardiol* 33 221 1974
  - 5 Schrank J P Slabaugh T K and Beckwith J R The incidence and clinical significance of ECG-VCG changes of myocardial infarction following aortocoronary saphenous vein bypass surgery *Am Heart J* 87 46 1974
  - 6 Manley J C and Johnson W D Effects of surgery on angina (pre and postinfarction) and myocardial function (failure) *Circulation* 46 1208 1972
  - 7 Van Heeckeren D W and Ankeney J L Aortocoronary graft patency related to perioperative myocardial infarction *Circulation* 47 (Suppl IV) IV 226 1973
  - 8 Dreifus L Cannarozzi N and Rabbino M Electrocardiographic alterations following prosthetic valve replacement *Circulation* 29 and 30 (Suppl III) III 70 1964
  - 9 Hultgren H N Hubis H and Shumway N Cardiac function following prosthetic aortic valve replacement *Am Heart J* 77 585 1969
  - 10 Bassam M M Oatfield R Hoffman I Matloff J and Swan H J C New Q waves after aortocoronary bypass surgery Unmasking of an old infarction *N Engl J Med* 290 349 1974
  - 11 Assad Morell J L Gau G T Frye R Connolly D Davis G D and Danielson G K Relation of early postoperative myocardial infarction to patency of aortocoronary bypass grafts and to ungrafted coronary arteries *Am J Cardiol* 35 767 1975
  - 12 Morton II and Morch J Myocardial infarction in coronary artery surgery *Circulation* 49 and 50 (Suppl III) III 137 1974
  - 13 Codd J E Kaiser G E Barner H B Millman V L and Miens R D Aortocoronary bypass grafting incidence of myocardial infarction *Circulation* 49 and 50 (Suppl III) III 166 1974
  - 14 Rose M R Glassman E Isom O W and Spencer F C Electrocardiographic and serum enzyme changes of myocardial infarction after coronary artery bypass surgery *Am J Cardiol* 33 215 1974
  - 15 Fruehan C T Johnson J W Potts J L Smulyan H Parker F B Jr and Eich R H Follow up catheterization of patients with myocardial infarction during coronary artery bypass surgery *Am Heart J* 91 186 1976
  - 16 Brewer D Bilbro R H and Bartel A G Myocardial infarction as a complication of coronary bypass surgery *Circulation* 47 58 1973
  - 17 Sones F M D and Shirey E K Cine coronary arteriography *Mod Concepts Cardiovasc Dis* 31 735 1962
  - 18 Judkins M P Selective coronary arteriography I A percutaneous transfemoral technique *Radiology* 89 615 1967
  - 19 Hambv R I Tabrah F Aintablian A Hartstein M L and Wisoff G H Left ventricular hemodynamic and contractile pattern after aortocoronary bypass surgery Factors affecting reversibility of abnormal left ventricular function *Am Heart J* 88 149 1974
  - 20 Herman M V Heimle R A Klein M D and Gorla R Localized disorders in myocardial contraction Asynergy and its role in congestive heart failure *N Engl J Med* 277 222 1967
  - 21 Bruschke A V G The diagnostic significance of the coronary arteriogram A study of its value in relation to other diagnostic methods *Utrecht 1970 Krentz m Zonn NY*
  - 22 Aintablian A Hamby R I, and Garsman J Correlation of heart size with clinical and hemodynamic findings in patients with coronary artery disease *Am Heart J* 91 21 1976
  - 23 Blackburn H Keys A Simonson E et al The electrocardiogram in population studies classification system *Circulation* 21 1160 1960
  - 24 Wisoff G Aintablian A Hartstein M L and Hamby R I Unified diagnostic and surgical approach to unstable angina *Ann Thorac Surg* 18 472 1974
  - 25 Kanjal S Reisman D Kouchoukos N and Sheffield L T Ischemic myocardial injury following aortocoronary bypass surgery *Chest* 67 20 1975
  - 26 Madras J E Chahine R A Gorlin R and Blacklow D J A comparison of transmural and nontransmural acute myocardial infarction *Circulation* 49 488 1974
  - 27 Grace J W (Editorial) Intermediate coronary care units revisited *Chest* 67 510 1975
  - 28 Conde C A Meller I Espinoza I Donoso E and Dack M Disappearance of abnormal Q waves after aortocoronary bypass surgery *Am J Cardiol* 36 889 1975
  - 29 Zelt M J Friedberg D King F Manley C Huston J D Reappearance of anterior QRS forces after coronary bypass surgery *Am J Cardiol* 36 163 1975
  - 30 Sternberg L Wisnietki A J Ulyot D J and Gerts W E Significance of new Q waves after aortocoronary bypass surgery correlation with changes in ventricular wall motion *Circulation* 52 1037 1975
  - 31 Blumenthal M R Wang H H, Pang Lu L M Experimental coronary artery occlusion and release Effects of enzymes electrocardiograms myocardial contractility and reactive hyperemia *Am J Cardiol* 36 225 1975
  - 32 Castellanos A Jr Lemberg L Post infarction conduction disturbances in vectorcardiography 1965 by Hodman I and Taylor R C Amsterdam 1965 North Holland Publishing Company pp 219 225

# Silent myocardial ischemia during and after exercise testing in patients with coronary artery disease\*

H Eugene Lindsey Jr MD  
Peter F Cohn MD  
Boston Mass

During exercise testing subjective symptoms of chest pain can often be related to objective evidence of myocardial ischemia when ST segment depression or elevation appears on the ECG.<sup>1</sup> Frequently however individuals with coronary artery disease have ischemic ECG responses to exercise testing without experiencing angina or its equivalents<sup>2-4</sup> indicating that there may be silent or asymptomatic myocardial ischemia just as there may be silent myocardial infarction.<sup>5</sup> Because the clinical and angiographic features of asymptomatic and symptomatic myocardial ischemia have not been compared in detail in previous exercise studies we studied the subjective as well as the objective responses to exercise testing in a group of patients with exercise induced ischemic ST changes in whom coronary artery disease was demonstrated by angiography.

## Methods

**Patient selection** In evaluating the phenomenon of silent myocardial ischemia we studied the exercise responses of 232 consecutive patients (tested between 1972 and 74) with chest pain syndromes who were free of concomitant valvular pericardial or congenital heart disease. One hundred eighty four patients had angiographically determined coronary artery disease and 48

had normal coronary arteriograms. Because of the difficulty in relating the presence or absence of chest pain to myocardial ischemia during a negative exercise test we were most interested in the patient who had an abnormal or positive exercise test. As expected from prior studies<sup>1</sup> only about 20 per cent of the patients with normal coronary arteriograms had a positive exercise test a number (11) too small for meaningful analysis. Therefore the present report concerns only the subgroup of 122 consecutive patients with coronary artery disease and an abnormal ECG response to exercise testing. These 122 consecutive patients all had clinically stable coronary artery disease (defined for this study as  $\geq 75$  per cent stenosis in the diameter of one or more of the three coronary arteries or their major branches) and neither left bundle branch block nor other disorders which might affect interpretation of the post exercise ECG<sup>6</sup> such as alcoholism, thyroid disease, valvular or pericardial heart disease or electrolyte abnormalities. Patients were queried (and their medical records examined) to determine whether they had a history of typical angina pectoris or a prior myocardial infarction or manifested signs of clinical congestive heart failure, hypertension (blood pressure  $> 140/90$  at any time) or hyperglycemia (fasting or two hour postprandial blood sugar  $> 120$  mg per cent) or were taking a digitalis preparation or propranolol. Patients who were on propranolol had their medication held for 24 to 36 hours prior to exercise testing.

**Exercise testing** Each patient was evaluated by one or more exercise tests on the day prior to angiography. The exercise protocol consisted of a double two step test for which the end point was chest pain (or its usual equivalent in each

From the Cardiovascular Division, Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass. Supported by United States Public Health Service Grants No HL 11306 and HL-7049.

Received for publication Oct. 14, 1976.

Accepted for publication Nov. 12, 1976.

Reprint requests: Peter F. Cohn MD, Cardiovascular Division, Peter Bent Brigham Hospital, 771 Huntington Ave., Boston, Mass. 02115.

Presented at the Fifty-eighth Annual Scientific Sessions of the American Heart Association, Anaheim, California, November 1975.

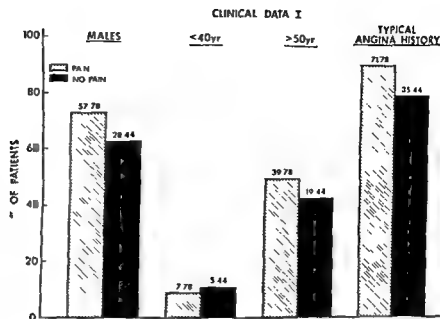


Fig 1 Sex distribution age and history of typical angina in patients with and without angina during or after exercise testing

patient) or completion of the test. Standard 12 lead ECGs were recorded with patients in the supine position before immediately after and three five and eight minutes after the test. A two step test was considered positive if there was new or additional J point depression  $\geq 0.5$  mm with a flat or depressed ST segment in any lead for at least 80 milliseconds immediately after and up to 8 minutes post exercise. If the test was negative or equivocal a bicycle ergometer test was performed after a 30 to 60 minute rest period. Patients were exercised with a bicycle ergometer at an initial work load of 300 k p m and this load was increased every three minutes by 150 k p m until 85 per cent of the maximum predicted heart rate was reached or symptoms forced the patient to stop. Lead  $V_3$  was monitored during the exercise test and recorded at minute intervals, and the standard 12 lead ECG was recorded at the same time intervals as the two step test. A bicycle test was considered positive if the ST segment depression was  $\geq 1.0$  mm during or up to 8 minutes post exercise. During and after the test patients were queried as to the presence of chest pain or jaw pain, pressure tightness or discomfort as well as fatigue or dyspnea.

**Coronary angiography** Coronary angiograms were recorded on 16 mm cine film in multiple projections using the Sones or Judkins technique. They were interpreted by consensus of two or more members of the senior cardiology staff usually without prior knowledge of whether the exercise test resulted in pain or not.

**Left ventriculography** Left ventriculograms were obtained in the right anterior oblique projection using multi holed catheters and power injections of 40 to 50 ml of 76 per cent meglumine sodium diazotrate. Volumes and ejection fractions were calculated by standard area-length methods utilized in our laboratory and reported in detail previously.<sup>8</sup>

## Results

**Frequency of angina in patients with positive exercise tests** Seventy eight of the 122 patients with positive exercise tests experienced angina or its usual equivalents. Forty four patients had no such symptoms but 12 of these 44 pain free patients had other symptoms which forced them to stop their tests. Three stopped because of shortness of breath and nine stopped because of generalized fatigue. The remaining 32 patients stopped only because they had completed the two step test or achieved 85 per cent of their predicted heart rate on the bicycle test.

### Comparison of subgroups with and without angina

**1 Age and sex distribution (Fig 1)** Seventy three per cent of the patients with pain were males compared to 54 per cent of the patients without pain (pNS). Mean age in the patients with pain was  $49 \pm 4$  (SEM) years and  $47 \pm 3$  years in the non pain group (pNS). The percent

Statistical significance determined by t test all other comparisons were by chi square tests

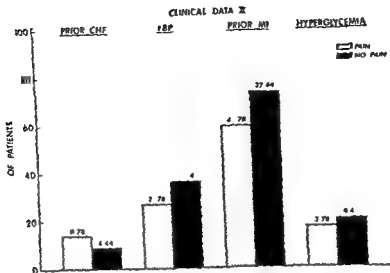


Fig 2 Frequency of congestive heart failure (CHF) hypertension (TBP) myocardial infarction (MI) and hyperglycemia in the two subgroups of patient

ages of patients in the < 40 and > 50 age groups were also similar

2 *Prior history of typical angina (Fig 1)* When the two subgroups were compared there was no statistically significant difference (91 per cent vs 80 per cent) in the frequency of a history of typical angina pectoris (exertion related chest discomfort promptly relieved by rest and/or nitroglycerin). Further analysis of the pain patterns indicated that there were similar numbers of NYHA Class III and Class IV patients in each subgroup

3 *Clinical congestive heart failure (Fig 2)* In each subgroup there were statistically similar numbers of patients with overt clinical congestive heart failure (14 per cent vs 9 per cent)

4 *Hypertension (Fig 2)* There were similar percentages of patients in each group with blood pressure higher than 140/90 mm Hg or a prior history of treated hypertension (27 per cent vs 36 per cent)

5 *Prior history of myocardial infarction (Fig 2)* Prior transmural or non transmural myocardial infarction (by history of ECG and/or cardiac enzyme evolution) was a common finding in this study but the frequency was statistically similar in each group of patients (59 per cent vs 73 per cent)

6 *Hyperglycemia (Fig 2)* The frequency of hyperglycemia and/or treated diabetes mellitus was similar in each group (17 per cent vs 20 per cent)

7 *Drug therapy (Fig 3)* Relatively small but almost equal numbers of patients were taking digitalis preparations prior to the study (18 per cent vs 16 per cent). As noted earlier propranolol was held for 24 to 36 hours prior to the exercise test and angiography. Forty seven per cent of the patients with pain were taking this drug compared to 36 per cent of the pain free group (pNS)

8 *Resting ECG (Fig 4)* The frequency of normal control ECGs with minor ST T abnormalities and ECGs diagnostic of prior transmural myocardial infarction were almost identical in the group with chest pain on exercise testing compared to the group without pain

9 *Angiographic findings (Fig 5)* Multivessel disease was a frequent finding in these patients (83 per cent vs 75 per cent pNS) as was the frequency of collateral vessels (62 per cent vs 70 per cent pNS). Impaired left ventricular function (defined as an ejection fraction less than 50%) was less common but was found with nearly equal frequency in both subgroups (24 per cent vs 30 per cent pNS)

10 *Exercise tests (Fig 6)* Exercise tests were analyzed to determine the maximum heart rate and the extent of the ischemic response. There were nearly equal numbers of patients in each group who had heart rates greater than 120 recorded during or immediately after exercise (50 per cent vs 43 per cent) suggesting equivalent degrees of stress. The frequency of strongly posi



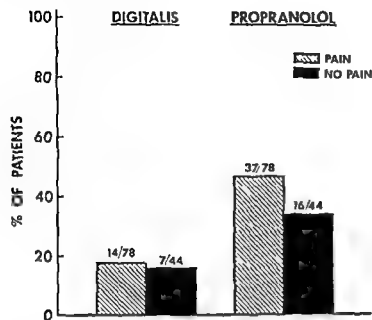


Fig 3 Use of digitalis and propranolol by the patients in the study

tive exercise tests (greater than 2 mm ST segment depression in any lead) was 42 per cent vs 41 per cent. In addition the lead location of the most positive response was also similar in both groups as was the post exercise time interval in which the maximum ST depression developed. Finally, the numbers of patients tested by only the double two step test versus those with additional bicycle ergometry was similar in each group with 64 per cent of the patients with pain having only a double two step test compared to 70 per cent of the pain free group.

In addition to the above analyses, various combinations such as hypertension and hyperglycemia were also compared with no significant differences noted between the two groups.

## Discussion

The present report concerns a group of 122 patients with coronary artery disease and an abnormal ECG response to exercise testing and examines their subjective response to presumed myocardial ischemia. In this study clinical and angiographic findings in the 78 patients with anginal pain or its equivalents during or after a positive exercise test were compared to the 44 patients without such symptoms. The two subgroups in the present study were shown to be similar statistically in selected aspects of their clinical histories, resting ECGs, technical aspects of exercise testing, exercise test results, extent of disease by angiography, and left ventricular function. A majority of the patients in both groups

had a history of angina that could be described as typical, but this occurred as frequently and with the same severity in both subgroups. Similarly, patients with myocardial infarction by history and by resting ECG were found with similar frequency in both groups and the group without chest pain was not comprised primarily of those patients whose marker for coronary artery disease had been a myocardial infarction rather than angina. Since diabetes mellitus and hypertension have a higher than expected incidence in patients with clinically unrecognized myocardial infarction<sup>3</sup> one might ascribe differences in the frequency of pain free exercise tests to differences in the numbers of the hyperglycemic and hypertensive patients in the two groups, but no such differences were found. The resting ECGs were also examined in the two groups. Although the presence of prior ST-T abnormalities might be expected to cause some difficulties in interpreting post exercise changes and possibly result in false positive (as well as false negative) results, patients with ST-T abnormalities were equally distributed between the two groups. Drug therapy might also contribute to problems in interpreting ECG changes as well as modifying the subjective response to ischemia, yet similar numbers of patients in each group had been on propranolol or digitalis preparations prior to hospitalization and propranolol was routinely held in this group of clinically stable patients for 24 to 36 hours prior to exercise studies. Analysis of the exercise test results shows that patients with pain did not have more strongly ischemic responses than patients without pain nor did the latter group have a reduced prevalence of lower exercise or post exercise heart rates, which would have suggested a less stressful test. The lead location of the most positive response was similar in both groups. Also, there were similar numbers of patients in each group tested by both bicycle ergometry and two step tests so that the mechanisms of testing should not have affected the results. The frequencies of multivessel disease and collateral circulation were the same in both groups and impaired ventricular function (decreased ejection fraction or clinical heart failure) was not related statistically to either the presence or absence of pain with exercise. Various combinations of clinical and angiographic parameters were also compared in the two groups and again no significant differences were found.

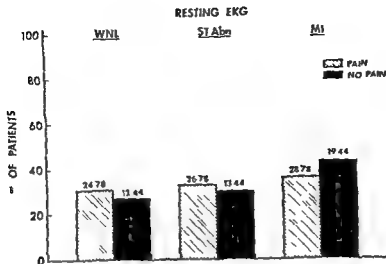


Fig 4 Frequency of various ECG findings at rest in the two subgroups of patients WNL = normal ST Abn = nonspecific ST-T abnormalities MI = myocardial infarction

The conclusion that only the subjective recognition of ischemic pain differentiated the patients in these two groups seems to be justified by the clinical ECG and angiographic parameters that were examined but several qualifications should be considered. First dyspnea has been reported to be an anginal equivalent<sup>8</sup> and three of the 44 pain free patients did complain of shortness of breath when they stopped their exercise test. Inclusion of these patients in the symptomatic subgroup did not result in any significant differences nor would inclusion of another nine patients with fatigue as their reason for stopping the test. We are still left with 32 patients (or 26% of the total group) without overt symptoms—assuming the veracity of their histories. Second it is possible that had all patients been exercised on a more rigorous exercise protocol more would have experienced symptoms. The difference probably would not have been marked however since Bartel and associates<sup>9</sup> using graded treadmill tests reported 17% pain free coronary patients with positive tests. Third we did not conduct pain threshold tests to determine if our pain free group actually had a higher than normal pain threshold. Fourth patients may have experienced truly unusual anginal equivalents without either they or the investigators being aware of them. Finally blood pressure determinations during exercise were not available in most patients and thus differences in pressure-rate products between the two groups could not be compared. These qualifi-

cations notwithstanding our results and those of the Duke University series<sup>10</sup> (as well as the studies dealing only with asymptomatic individuals<sup>3,4</sup>) indicate that a considerable number of patients with coronary disease may have ECG evidence of exercise induced myocardial ischemia without angina or its usual equivalents. These studies plus those employing ambulatory ECG monitoring to detect ischemic heart disease<sup>1</sup> suggest that in some patients the anginal warning system (resulting from a combination of humoral neural and psychologic factors) is temporarily or permanently defective. The presence of such a defective warning system may help to explain why the initial manifestation of coronary artery disease in some individuals is myocardial infarction or sudden death and why identification of such individuals before the occurrence of a morbid event can be difficult.<sup>1</sup>

### Summary

Although many patients with coronary artery disease (CAD) have a positive exercise test without pain the frequency and significance of this silent ischemia is unclear. Therefore we studied 122 consecutive clinically stable patients with angiographically defined CAD (> 75 per cent luminal stenosis) and a positive exercise test. Seventy eight patients had pain or anginal equivalent during or after a positive exercise test. 44 did not including 32 (26 per cent) with no symptoms at all. Patients were evaluated as to age sex

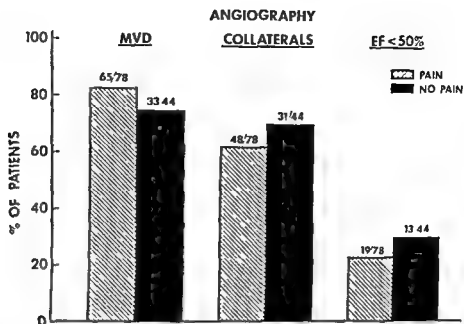


Fig 5 Frequency of multivessel disease (MVD) collateral vessels and poor ventricular function in the two subgroups of patients EF = ejection fraction

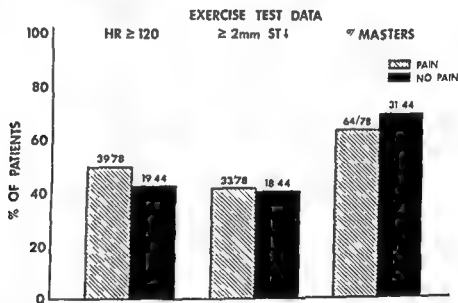


Fig 6 The two subgroups are compared for frequency of maximum heart rate > 120 beats/minute with exercise markedly positive post exercise ECG (> 2 mm ST segment depression) and two step (Master's) testing

prior myocardial infarction congestive failure, hypertension diabetes mellitus, and digoxin or propranolol therapy—in addition to anginal symptoms before during or after the exercise itself. Extent of CAD presence of collaterals and left ventricular ejection fraction were also determined. All exercise tests were evaluated for evidence of ST-T abnormalities or prior infarction on the control ECG as well as peak heart rate during exercise and post exercise degree of ST segment depression. There were no significant differences between patients with and without exercise induced pain in regard to any of the clinical and angiographic features noted above.

demonstrating that silent myocardial ischemia during or after exercise testing is not uncommon and is not readily attributable to any obvious clinical or catheterization findings. Further studies are necessary to determine if patients with evidence of "silent" myocardial ischemia are especially prone to sudden death.

#### REFERENCES

1. Bruce RA and Hornsten TR. Exercise stress testing in evaluation of patients with ischemic heart disease. *Prog Cardiovasc Dis* 11:371 1969.
2. Kattus AA, Jorgensen C II, Worden RF and Alvaro AD. ST segment depression with near maximal exercise in detection of preclinical coronary heart disease. *Circulation* 44:58, 1971.

3. Froelicher V F, Yanowitz F G, Thompson A J, and Lancaster M C. The correlation of coronary angiography and the electrocardiographic response to maximal treadmill testing in 76 asymptomatic men. *Circulation* 48:97 1973
4. Borer J S, Brenske J F, Redwood D R, Itskowitz S B, Passamani E R, Store N I, Richardson J M, Levy R I, and Epstein S M. Limitations of the electrocardiographic response to exercise in predicting coronary artery disease. *N Engl J Med* 293:367 1975
5. Margolis J R, Kannel W B, Feinleib M, Dawber T R, and McNamara P M. Clinical features of unrecognized myocardial infarction—silent and asymptomatic. *Am J Cardiol* 32:1 1973
6. Kemp H G Jr, Volonas P S, Cohn P F, and Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 55:735 1973
7. Lepeschkin E, and Barawicz B. Characteristics of true positive and false positive results of electrocardiographic two step test. *N Engl J Med* 258:511 1958
8. Cohn P F, Gorlin R, Adams D F, Chahine P A, Volonas P S, and Herman M V. Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease. *Am J Cardiol* 33:1 1974
9. Kennedy H L, and Underhill S J. Ischemic ST segment depression and dyspnea. *AM HEART J* 80:544 1975
10. Bartel A G, Behar V S, Peter R H, Orgain E S, and Kong Y. Graded exercise tests in angiographically documented coronary artery disease. *Circulation* 49:348 1974
11. O'Rourke R A., Ross J R Jr. Ambulatory electrocardiographic monitoring to detect ischemic heart disease. *Ann. Intern. Med* 81:690 1974
12. Gorlin R. Pathophysiology of cardiac pain. *Circulation* 32:138 1965
13. Cohn, P F. Severe asymptomatic coronary artery disease. A diagnostic, prognostic and therapeutic puzzle. *Am J Med* 62:580 1977

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material."

# Bacterial endocarditis An analysis of factors affecting long-term survival

K Mills McNeill, Ph D, M D

James E Strong, Jr, M D

W R Lockwood, M D

Jackson Miss

In a review of the experience with bacterial endocarditis at the University of Mississippi Medical Center (UMMC) during the interval 1955 to 1959 Jackson and Allison<sup>1</sup> reported that only 50 per cent of their patients survived 12 months or longer, a figure well below the 90 per cent given by Weinstein and Rubin<sup>2</sup> in a recent report. It was of interest, therefore, to study the more recent experience at the UMMC. It is the purpose of this paper to report some aspects of the experience with bacterial endocarditis in adults who were treated in the UMMC during the interval from January 1, 1960 through June 30, 1974. Emphasis is placed on analysis of factors related to prognosis.

## Material and methods

The individuals included in this study were all admitted to the medical wards of the UMMC during the interval from January 1, 1960 until July 30, 1974. The diagnosis of bacterial endocarditis was considered adequately documented for the purposes of this study if bacteria were recovered from the blood and the clinical picture was suggestive or if in the presence of sterile blood cultures the clinical picture was classic, or if there was confirmation by autopsy. Cases were excluded if the patient's condition one year after admission to the UMMC was unknown.

A total of 194 cases were obtained by review of the records of the infectious disease division from

discharge diagnoses and by review of all autopsies performed during the study period. A total of 113 patients met our criteria but, of these five represented endocarditis that occurred after cardiac surgery and were eliminated. Six patients having received no treatment, were diagnosed at autopsy, leaving a total of 102 treated cases.

Follow up data until time of death or end of the study were obtained on all 102 patients who were felt to have adequate confirmation of bacterial endocarditis, but as the earlier patients were followed much longer than those treated in the last few years of the study, emphasis will be on the status of the individual one year after the diagnosis was made. These patients were then examined relating longevity from the time of illness to the following: (1) infecting organisms, (2) age at time of diagnosis, (3) sex of patient, and (4) the presence of pre existing heart disease. Autopsy data (36 patients) were examined with emphasis on valve involvement, pre existing heart disease, and complications of endocarditis.

## Treatment

Each patient received an antimicrobial regimen appropriate for the treatment of endocarditis. When the organism was known the antimicrobial drugs were selected on the basis of the sensitivities as measured in the laboratory. In as much as penicillin sensitive organisms were isolated most often, most patients were treated with intravenously administered penicillin G plus intramuscular streptomycin. When the organism was not recovered from the bloodstream, large doses of penicillin G plus streptomycin were used. Bacteriological cure as shown by disappearance of bacteria from the blood plus deference and

From the Department of Medicine, University of Mississippi Medical Center, Jackson, Miss.

Received for publication Oct. 18, 1976.

Accepted for publication Jan. 7, 1977.

Reprint requests: W. R. Lockwood, M.D., University of Mississippi Medical Center, 2500 N. State St., Jackson, Miss. 39216.

other signs of clinical improvement was achieved in most cases. In two individuals therapy was not successful in eradicating the infecting organism. One of these a 37 year old white female with enterococcal disease died after 142 days of treatment that included penicillin G vancomycin ristocetin streptomycin erythromycin tetracycline and chloramphenicol in several combinations. The other a 62 year old white male with *Streptococcus viridans* disease was treated for 37 days with penicillin G streptomycin and probenecid but 14 days later the organism was again present in his blood. An additional 43 days of treatment resulted in clearing the infection but he died of congestive heart failure six months later. A third patient addicted to heroin deserted three times prior to completion of her regimen for treatment of *Staphylococcus aureus* disease and was finally treated for six consecutive weeks with methicillin plus streptomycin. She died eight years later but the cause of her death is unknown.

## Results

Over all 100 patients died within 30 days of admission and an additional 32 patients died within the first year after the onset of their illness. Thus a total of 58 patients or 56 per cent of the group died in the first 365 days leaving only 44 individuals or 44 per cent as survivors.

Seventeen different infecting organisms were identified in the 102 patients studied. The number of patients infected with each organism and the number of these surviving at least for one year are seen in Table I. Five patients had multiple organisms identified on blood cultures while 16 patients had negative blood cultures.

Fig 1 relates one year survival in 88 patients with frequently encountered organisms. Of all patients with alpha hemolytic *Streptococcus* identified on blood culture approximately 72 per cent survived one year whereas only 27 per cent of patients with *Staphylococcus aureus* survived one year and 50 per cent of patients with *Enterococcus* identified on blood culture survived one year. Of the four patients with *Staphylococcus epidermidis* identified on blood culture none were alive after 365 days. Sixteen patients had no organisms identified on blood culture and of these five patients or 31 per cent were alive at one year. Five patients had multiple organisms identi-

**Table I** Results of blood cultures from 102 cases of bacterial endocarditis

| Organism                          | Number times recovered | Number of patients surviving 365 days |
|-----------------------------------|------------------------|---------------------------------------|
| <i>Streptococcus viridans</i>     | 32                     | 12                                    |
| <i>Enterococcus</i>               | 10                     | 3                                     |
| <i>Staphylococcus aureus</i>      | 15                     | 4                                     |
| <i>Staphylococcus epidermidis</i> | 4                      | 0                                     |
| <i>Streptococcus mutans</i>       | 1                      | 0                                     |
| <i>Pseudomonas</i>                | 1                      | 0                                     |
| Group A beta <i>Streptococcus</i> | 2                      | 0                                     |
| <i>Herellea</i>                   | 1                      | 0                                     |
| <i>Pneumococcus</i>               | 4                      | 1                                     |
| Non hemolytic                     | —                      | —                                     |
| <i>Streptococcus</i>              | 3                      | 0                                     |
| Anaerobic non hemolytic           | —                      | —                                     |
| <i>Streptococcus</i>              | 1                      | 1                                     |
| <i>Escherichia coli</i>           | 1                      | 0                                     |
| <i>Proteus</i> species            | 1                      | 1                                     |
| <i>Corynebacterium</i>            | 1                      | 1                                     |
| <i>Diphtheroid</i>                | 1                      | 1                                     |
| <i>Streptococcus salivarius</i>   | 1                      | 1                                     |
| <i>Hemophilus parainfluenzae</i>  | 1                      | 1                                     |
| None                              | 16                     | 4                                     |
| Multiple organisms†               | 5                      | 3                                     |

Previously reported

†Identities included in list above

fied on blood culture and all five were alive after 365 days.

**Pre-existing heart disease** Pre existing heart disease was present in a group of 97 patients. In Fig 2 this is related to the infecting organism. It is seen that 94 per cent of patients with alpha hemolytic streptococcus identified on blood culture had pre existing heart disease. All 10 patients with *Enterococcus* documented as the infecting organism were found to have pre existing cardiovascular disease. Sixty seven per cent of patients with *Staphylococcus aureus* endocarditis had a prior history of heart disease whereas 94 per cent of patients with no organism identified had prior heart disease. Seventy one per cent of those with other organisms had prior heart disease. Two of the four patients with multiple organisms identified on blood culture had prior heart disease.

Rheumatic heart disease accounted for 75 per cent of the patients identified with pre existing heart disease whereas congenital heart disease accounted for 9 per cent. Other forms of heart

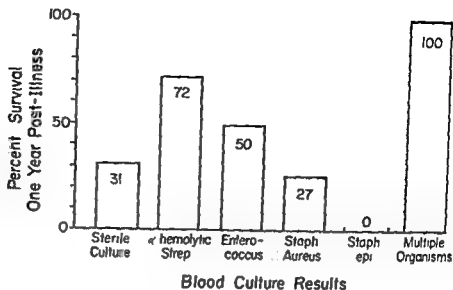


Fig 1 Per cent surviving one year vs causative organism in 102 cases of bacterial endocarditis

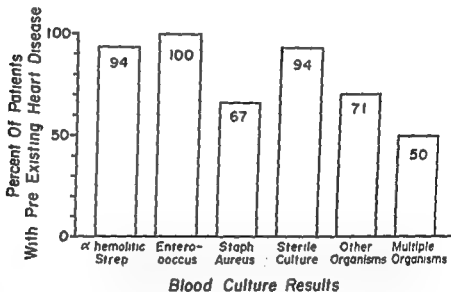


Fig 2 The per cent of the patients with pre existing heart disease is shown vs the causative organism in 102 cases of bacterial endocarditis

disease mostly arteriosclerotic and hypertensive heart disease accounted for 12 per cent

**Longevity vs sex of patient** Fig 3 reflects relationship of the sex of the patient to survival time. Of the 58 males (average age 44.11 years) and 43 females (average age 35.2 years) represented it is noted that an almost identical percentage died in the first 30 days of their illness. Thirty two per cent of males and 33 per cent of females died during this time. At six months 48 per cent of males and 58 per cent of females remained alive. This 10 per cent difference remained until approximately the fourth year of follow up with both groups experiencing approximately 7 per cent mortality per year. By the fifth year of follow up 19 per cent of the original group of males and 20 per cent of the females remained alive. Both

groups continued to experience 3 per cent mortality yearly with 6 per cent of females and 2 per cent of males being alive in the eleventh year after their illness.

**Longevity vs age at time of illness** The 102 patients are grouped according to age in Fig 4. Twelve per cent of patients were from 16 to 19 years old. Twenty per cent were in their third decade at the onset of their illness. Eighteen per cent were 30 to 39 years of age and 17 per cent were 40 to 49 years old. The sixth decade represented 14 per cent of the total group. Twelve per cent were 60 to 69 years old, and 0 per cent of the entire group was greater than seventy years old.

It was noted above that in this group of 102 patients the over all one year survival was found to be 44 per cent. When this was examined in

relation to age at the time of illness it was observed that the highest one year mortality occurred in the fifth and sixth decades with 37 per cent and 21 per cent surviving respectively. The seventh decade representing 12 per cent of the total was found to have 42 per cent one year survivors while the lowest mortality was found in the third decade with 67 per cent surviving one year. Both the 16 to 20 year age group and the greater than 70 year age group had identical one year survivals of 50 per cent. The fifth decade had 53 per cent survivors.

**Autopsy data** Autopsy data was available for 36 patients. In these patients' postmortem cultures confirmed antemortem cultures in 25 per cent. In another 11 per cent the organism was isolated only at time of autopsy.

The mitral valve was found at autopsy to be involved in 33 per cent of the cases, the aortic valve in 33 per cent of the cases and both aortic and mitral valve in 26 per cent of the cases. In one patient only the left atrium was involved while another patient had involvement of both the aortic and tricuspid valves.

Pre existing rheumatic valve disease was noted in 22 per cent of the autopsies while the presence of arteriosclerotic heart disease was documented in 17 per cent of the autopsy protocols.

An acute myocardial infarct was noted in six of the autopsied patients and emboli were noted in the coronary arteries of four of these patients. Pulmonary edema, liver congestion and other autopsy findings compatible with congestive heart failure were found in 42 per cent of the autopsies. There were emboli in the vessels of the kidney, spleen and other sites in 61 per cent of autopsies. Glomerulonephritis was described in only 19 per cent of the autopsied patients.

An accompanying meningitis was noted in three patients. One case of myocardial abscess and one of myocarditis were described.

### Discussion

Weinstein and Rubin<sup>2</sup> have stated that the survival in infective endocarditis approaches 90 per cent. Others have stated that 82 per cent of patients followed for five years after discharge remained alive. In our group of 102 patients the survival rates both at one year and at the end of a 14 year follow up period were much lower than in these reports. We found a 1 year mortality rate of 56 per cent which is quite similar to the 50 per

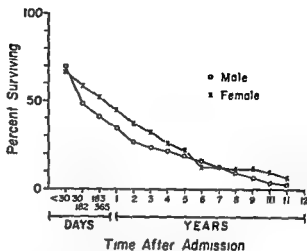


Fig 3 Males and females were nearly equally represented (58 and 43 respectively). The difference in deaths during the 5 years after admission is probably accounted for by the men being slightly older than the women.

cent mortality rate reported by Jackson and Allison in an earlier study at this institution and compares closely with the 45 per cent survival rate reported by Mills and associates.<sup>4</sup>

Thirty three per cent of our patients were infected with *Streptococcus viridans*. These patients had a 72 per cent one year survival rate. A recent review<sup>5</sup> has noted that the incidence of *Streptococcus viridans* endocarditis presently seems to account for 35 per cent to 48 per cent of all patients with endocarditis. This contrasts with 79 per cent of cases of infective endocarditis due to this organism in the pre antibiotic era. In a review in 1962 Vogler and colleagues found 73 per cent of patients with *Streptococcus viridans* to be hospital survivors. This is compared to 69 per cent of our patients who were one year survivors. However after 11 years follow up it is interesting that only 36 per cent of our patients with *Streptococcus viridans* endocarditis remained alive. This may represent the severity of the underlying valvular disease which 93 per cent of patients with *Streptococcus viridans* were believed to have.

Previous studies have shown a striking increase in survival of patients with *Streptococcus viridans* and in those with sterile blood cultures during the antibiotic era.<sup>6</sup> With the exception of those patients infected with *Staphylococcus epidermidis* our highest mortality rate was observed in the group of patients with sterile blood cultures. Only 28 per cent of these patients



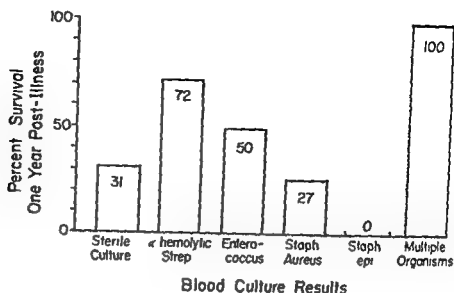


Fig 1 Per cent surviving one year vs causative organism in 102 cases of bacterial endocarditis

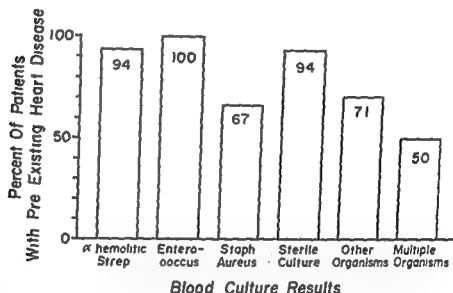


Fig 2 The per cent of the patients with pre existing heart disease is shown vs the causative organism in 102 cases of bacterial endocarditis

disease, mostly arteriosclerotic and hypertensive heart disease accounted for 12 per cent

**Longevity vs sex of patient** Fig 3 reflects relationship of the sex of the patient to survival time. Of the 58 males (average age 44.6 years) and 43 females (average age 35.2 years) represented it was noted that an almost identical percentage died in the first 30 days of their illness. Thirty two per cent of males and 33 per cent of females died during this time. At six months 48 per cent of males and 58 per cent of females remained alive. This 10 per cent difference remained until approximately the fourth year of follow up with both groups experiencing approximately 7 per cent mortality per year. By the fifth year of follow up 19 per cent of the original group of males and 20 per cent of the females remained alive. Both

groups continued to experience 3 per cent mortality yearly with 6 per cent of females and 2 per cent of males being alive in the eleventh year after their illness.

**Longevity vs age at time of illness** The 102 patients are grouped according to age in Fig 4. Twelve per cent of patients were from 16 to 19 years old. Twenty per cent were in their third decade at the onset of their illness. Eighteen per cent were 30 to 39 years of age and 17 per cent were 40 to 49 years old. The sixth decade represented 14 per cent of the total group. Twelve per cent were 60 to 69 years old and 6 per cent of the entire group was greater than seventy years old.

It was noted above that in this group of 102 patients the overall one year survival was found to be 44 per cent. When this was examined in

those individuals with bacterial endocarditis treated in one large medical center during the period January 1960 to June 1974 was poor over all with approximately 56 per cent dying within the first year after diagnosis. The deaths were due to either heart failure or complications secondary to embolic phenomena. Recently several patients have undergone valve replacement in an effort to avoid seemingly certain death from progressive cardiac failure. We as others believe the prognosis is thereby improved but long term follow up will be required to study the effect of this approach.

### Summary

The records of 108 patients treated for bacterial endocarditis were reviewed. Six were diagnosed at autopsy and had not been treated for endocarditis. Of the 102 treated patients, 32 died during the first 30 days and 32 more were dead by 365 days.

Although some reports indicate a much greater survival rate, our findings are more in keeping with those reports giving a rather poor long term outlook for patients with endocarditis.

We thank Mr. Al Sheffield of the Division of Public Health Statistics of the Mississippi State Health Department, Miss Betty Ezelle of the UMMC and many social workers and nurses of the State Health Department for their assistance.

### REFERENCES

1. Jackson J. P. and Allison F. Jr. Bacterial endocarditis. *South. Med. J.* 54:1331, 1961.
2. Weinstein L. and Rubin H. H. Infective endocarditis—1973. *Progr. Cardiovasc. Dis.* 16:239, 1974.
3. Volger W. H., Dorney E. R. and Bridges H. A. Bacterial endocarditis: A review of 148 cases. *Am. J. Med.* 32:910, 1962.
4. Mills J., Utley J. and Abbott J. Heart failure in infective endocarditis: Predisposing factors, course, and treatment. *Chest* 66:151, 1974.
5. Lockwood W. R., Lawson L. A., Smith E. L., McNeill K. M. and Morrison F. S. *Streptococcus mutans* endocarditis: Report of a case. *Ann. Intern. Med.* 80:369, 1974.

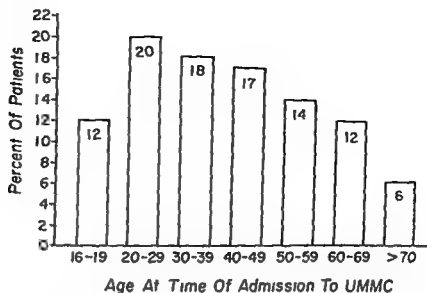


Fig 4 Age at time of admission of patients with bacterial endocarditis shows the disease present in all age groups studied with most cases during the third fourth and fifth decades

survived one year after hospitalization. It should be noted that anaerobic cultures were not obtained consistently and this may account for some of the negatives. Previous studies have shown the incidence of heart failure to be 60 per cent in patients with sterile blood cultures.<sup>4</sup> Of 19 patients with sterile blood cultures reported by Vogler and colleagues,<sup>5</sup> there were seven or 36 per cent hospital survivors. This high mortality rate may be attributed to the difficulty in selection of and the delay in starting adequate antimicrobial therapy under such circumstances.

Only 33 per cent of patients with *Staphylococcus aureus* in the present study survived one year after hospitalization. Prior to 1950 no survivors of *Staphylococcus aureus* endocarditis were noted.<sup>2</sup> Two recent reviews have shown the hospital survival of patients with *Staphylococcus* endocarditis to be approximately 30 per cent to 40 per cent,<sup>2,4</sup> with a 35 per cent incidence of severe heart failure developing within six months of the onset of illness.

All four of our patients with *Staphylococcus epidermidis* endocarditis died within the first year. It is noted by Weinstein and Rubin<sup>2</sup> that infection with *Staphylococcus epidermidis* was practically unknown prior to the antibiotic era and is usually seen in patients with underlying rheumatic heart disease.

One year survival of the eleven patients with enterococcal endocarditis was observed to be 50 per cent. Other observers have noted 77 per cent hospital survivors in a group of 13 patients with enterococcal endocarditis<sup>3</sup> and an incidence of

heart failure approaching 100 per cent in these patients.

It was surprising that all five of the patients with multiple organisms on blood culture survived the first year. The cause for this seemingly paradoxical observation is not known.

As stated above, 99 of the 108 patients included in this review had pre-existing heart disease. Rheumatic heart disease accounted for 77 per cent, while congenital heart disease accounted for only 9 per cent.

The slightly higher mortality rate of males throughout the follow-up period may be explained by the observation that the average age of the males was approximately 10 years greater than that of the females.

When the mortality figures are compared with the age of the patient at the time of illness, it can be seen that the highest mortality rate occurred in the sixth decade. Although this could be expected with advancing age, only 37 per cent of the patients aged 30 to 39 years survived one year after hospitalization. Perhaps a more severe form of valvular disease in younger individuals could account for this discrepancy. The third decade had the highest percentage of one year survivors and the lowest attrition rate, although it should be noted that only three of 21 original patients survived at the end of the study. In evaluating these findings it should be noted that some of the 25 survivors in all age groups were less than five years post diagnosis at the completion of the study period.

Our observations showed that the outlook for

exercise blood pressure and heart rate were recorded at minute intervals. Respiratory function tests were performed on the day of testing. The current chest x ray was compared to the immediate preoperative film.

The difference among the mean FAI values of the etiological groups and for valve types were tested using the Wilcoxon ranked sum test. A correlation coefficient was calculated for the relationship of FAI and time since operation.

## Results

The results of FAI for the three etiological groups have been plotted in Fig 1. The mean FAI for the Q fever group was  $9.6 \pm 12.1$ , for the bacterial endocarditis group it was  $24.1 \pm 14.6$  and for the rheumatic fever group it was  $24.8 \pm 10.5$ . The values for the Q fever group are significantly better than values for either the endocarditis group ( $p < 0.05$ ) or the rheumatic fever group ( $p < 0.05$ ).

The following mean FAI values were obtained from the valve types: Braunwald Cutter  $15.1 \pm 8.1$ , homograft  $28.1 \pm 22.1$ , fascia lata  $24.8 \pm 6$ , Lillehei-Kaster  $12.7 \pm 16$ . No significant difference was found between any of the groups. No correlations were found between the time since operation and FAI. There was no difference in blood pressure or heart rate response for the three groups.

The mean pre and postoperative cardiothoracic ratios for each group are shown in Table I.

The respiratory function tests were within normal limits for all patients thus excluding a respiratory cause for impaired maximal oxygen uptake.

## Discussion

There is a clear difference in exercise capacity between the groups of patients who had Q fever endocarditis and those groups who had bacterial endocarditis and rheumatic fever.

There is substantial evidence that permanent myocardial damage occurs as a direct consequence of bacterial endocarditis. Autopsies of patients suffering from bacterial endocarditis frequently show microemboli, scattered focal myocardial abscesses or diffuse interstitial myocarditis. Animal experiments have shown that the enzymes produced by bacteria responsible for the endocarditis are capable of causing a myocar-

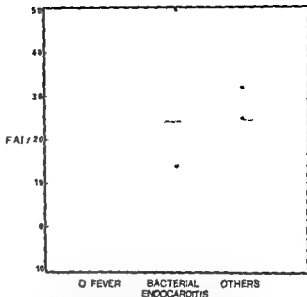


Fig 1 The functional aerobic impairment (FAI) values have been plotted for the three etiological groups. The horizontal bars indicate the mean of each group.

Table I Pre and postoperative cardiothoracic ratios for each group

| Etiology               | Cardiothoracic ratio |                |                                    |
|------------------------|----------------------|----------------|------------------------------------|
|                        | Pre operative        | Post operative | Mean difference ( $\pm$ std error) |
| Q fever*               | 56                   | 47             | $09 \pm 02$                        |
| Bacterial endocarditis | 57                   | 46             | $10 \pm 02$                        |
| Others                 | 57                   | 51             | $06 \pm 01$                        |

\*The ratio of mean change to its standard error for all three groups was to the order of 5:1.

ditis and eventual fibrosis. Acute experimental endocarditis is associated with mononuclear cell infiltrate and muscle degeneration in the myocardium associated with hemodynamic impairment.<sup>12</sup>

In rheumatic fever endocardium, myocardium and pericardium can be involved in the acute stage, most commonly all three in combination. Myocardial involvement can cause serious cardiac disability in heart failure in the acute stages. Aschoff bodies, the histologic hallmark of rheumatic fever, are found principally in the interstitial circular fibrous septa and in the connective tissue around blood vessels. Eventually these proliferative lesions are replaced by fibrous tissue so that

# Influence of etiology on the functional result of aortic valve replacement

K F Hossack MRACP

Graeme Neilson, FRACP, FRCP

Brisbane Australia

Surgical intervention in symptomatic aortic incompetence improves longevity when compared with the natural history of the disease.<sup>1,2</sup> The success of the operation in most reports has been based upon late survival statistics and cardiac functional classification before and after surgery.<sup>3,4</sup> More detailed postoperative assessment of patients following aortic valve replacement for isolated aortic incompetence has revealed residual left ventricular impairment.<sup>5</sup> Preoperative factors shown to influence late survival are cardiac size, congestive cardiac failure, and ventricular premature beats.<sup>6,7</sup>

In this study the effect etiology had on the functional result of aortic valve replacement for isolated aortic incompetence was examined. Maximal exercise testing on a treadmill was used as a means of comparison.

## Methods and Materials

Twenty five patients were studied. All patients had previously had aortic incompetence as their only valve lesion which had been assessed as severe. They were divided into three groups on an etiological basis. Seven had suffered from Q fever endocarditis, nine from bacterial endocarditis and a third group comprised eight patients who had suffered rheumatic valvular disease and one patient who had aortic wall disease associated with hypertension.

The diagnosis of Q fever endocarditis was

confirmed in each case by culturing *Coxiella burnetii* in guinea pigs inoculated with valve material removed at operation.

The duration of signs and symptoms before surgery in the Q fever and rheumatic group ranged between three months and 15 years the mean in both groups being 7.6 years. Seven of the nine patients in the bacterial endocarditis group had a very short duration of symptoms prior to valve replacement.

At operation a variety of valves were used. They included eight Braunwald Cutter prosthetic valves, seven homografts, six fascial lata and four Lillehei Kaster prosthetic valves. At the time of testing all valves were competent and no patient had clinical or radiological evidence of heart failure. There was no evidence of ischemic heart disease.

The interval between surgery and exercise testing in each group was

Q fever endocarditis—6 months to 52 months (mean 26 months)

Bacterial endocarditis—17 months to 60 months (mean 31 months)

Others—10 months to 64 months (mean 36 months)

Treadmill exercise testing was carried out according to the Bruce protocol.<sup>8</sup> All patients were exercised maximally, the indications for termination of exercise were, dizziness, dyspnea, leg fatigue or multiple ventricular ectopic beats. No patient developed chest pain with exercise. Bruce and colleagues<sup>9</sup> have shown that functional aerobic impairment (F A I) related to maximal oxygen uptake and hence to cardiac output.

By using the appropriate nomograms<sup>10</sup> the F A I value was obtained from the total duration of exercise performed on the treadmill. During

From the Cardiac Investigation Unit, The Prince Charles Hospital, Chermide, Australia.

Received for publication Oct 22 1976

Accepted for publication Jan 18 1977

Reprint requests: Dr Graeme Neilson, Medical Director, Cardiac Investigation Unit, The Prince Charles Hospital, Rode Road, Chermide, Q 4032, Australia.

# Coronary artery spasm and mitral valve prolapse

A J Buda MD  
D L Levene MD  
M G Myers MD  
A W Chisholm MD  
S J Shane MD

Toronto Ontario Canada

Mitral valve prolapse is a well recognized clinical entity occurring predominantly in females of virtually all ages. Commonly associated symptoms include chest pain, dyspnea, fatigue, palpitation, presyncope and syncope. The pathogenesis of these symptoms, particularly the symptom of chest pain, has remained poorly understood.

Several authors<sup>1</sup> have suggested that an ischemic process may be a possible cause of precordial pain in some patients with mitral valve prolapse. Since most individuals with this condition have normal coronary arteries at angiography,<sup>2</sup> we considered the possibility that coronary artery spasm may produce transient myocardial ischemia in association with mitral valve prolapse. The following study was therefore undertaken to examine the incidence of mitral valve prolapse in patients with chest pain who exhibited coronary artery spasm during selective coronary arteriography.

## Material and methods

The files of 745 patients investigated by selective coronary arteriography in the Cardiovascular Unit of Sunnybrook Medical Centre between 1969 and 1975 were reviewed for evidence of coronary artery spasm. This was defined for the purposes of this study as the visualization of a segmental or diffuse area of significant reduction

(70 per cent) in the coronary arterial lumen reversible either spontaneously or by the administration of vasodilating agents.

Ten patients representing 1.34 per cent of all those undergoing selective coronary arteriography were shown to have reversible coronary artery spasm as above defined by sequential coronary arteriography. All 10 patients had undergone investigation including right and left cardiac catheterization, left ventriculography, and selective coronary arteriography by Judkins technique—in that order—under mild sedation with diazepam.

The coronary arteriograms were performed with Renografin 76 and angiographic images were recorded on 35 mm film at 60 frames/second. In addition, two of the 10 patients had angiography images recorded on 70 mm film at 4 frames/second. Routine LAO and RAO projections were performed in all patients. Nitrates were not administered routinely prior to coronary arteriography.

The left ventricular cineangiograms were obtained in the 30 degree RAO projection.

These 10 coronary arteriograms were reviewed by three independent observers for evidence of unequivocal spasm as defined above. The left ventricular cineangiograms were reviewed by the same observers for abnormalities of left ventricular wall motion and evidence of mitral valve prolapse. The angiographic criteria for mitral valve prolapse were based on angiographic anatomic correlations previously described<sup>3,4</sup> in which prolapse of the middle scallop produced a central bulge overlying the left atrium in the RAO left ventricular cineangiogram. Prolapse of

From the Division of Cardiology, Sunnybrook Medical Centre, Toronto, Ontario, Canada.

Received for publication March 8, 1977.

Accepted for publication July 6, 1977.

Reprint requests: Dr. S. J. Shane, Cardiovascular Unit, Sunnybrook Medical Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 1A9.

0007-2566/78/0430-0045\$06.00/0 © 1978 The C.V. Mosby Co.

there is a diffuse increase in the amount of fibrous tissue present.<sup>11</sup>

*Coxiella burnetii*, the organism responsible for Q fever is an obligate intracellular parasite.<sup>12</sup> In the heart it is found only in the endothelial and serosal cells and does not invade the myocardial cells. The organism has not been shown to produce toxins.<sup>13</sup> In a recent review of Q fever endocarditis,<sup>14</sup> the indolent nature of the disease was emphasized and because of the biological properties of *Coxiella burnetii* it is unlikely to cause myocardial damage similar to that caused by bacteria.

The indication for aortic valve replacement in all patients was symptomatology accompanied by severe aortic incompetence assessed by catheter study. The cardiothoracic ratios indicated that the three groups were comparable on the basis of heart size. There was a significant reduction in heart size following operation, but not more marked in one group than another.

The preoperative duration of signs and symptoms were the same in the Q fever group and the rheumatic fever group. On the other hand the bacterial endocarditis group with a very short duration of history, performed much the same as the rheumatic group. These facts suggest that length of history and hence the hemodynamic abnormality is not important in the long term results of aortic valve replacement.

Following the successful aortic valve replacement, long term studies show that most patients achieve an improved cardiac functional classification after surgery and maintain this for a number of years.<sup>15</sup> This study confirms that there is no relationship between functional result and length of follow up.

Four different types of valves were used for the valve replacement. This reflects the changing approach to valve replacement in the unit. Initially fascia lata valves were used but when it became apparent that these valves developed incompetence after insertion homografts and Braunwald Cutter valves were used. Homografts were used in preference to prosthetic valves but the determining factor was the size of the aortic valve ring. Initially Braunwald Cutter valves were used but later Lillehei Kaster valves were the prosthetic choice. Although statistical analysis of the results for individual valves within etiological groups is not possible because of the small numbers it does not seem likely that there is any difference.

## Summary

The functional result of aortic valve replacement has been assessed in patients treated for isolated aortic incompetence. Using maximal oxygen uptake as an index of myocardial function, a significant difference ( $p < 0.05$ ) exists between the patients who had Q fever endocarditis on the one hand and those who had bacterial endocarditis or rheumatic fever on the other. We believe that permanent myocardial damage occurs as a result of bacterial endocarditis and rheumatic fever but because of the biological properties of *Coxiella burnetii* the myocardium is spared in Q fever endocarditis.

## REFERENCES

1. Rapaport E. Natural history of aortic and mitral valve disease. *Am J Cardiol* 35:221, 1975.
2. Galyean J H, Suzuki A, and Blake J M. Surgery for aortic valve disease. *AM HEART J* 88:683, 1974.
3. Shearn F C, Austen W G, Buckley M J, Mundth, E G, Scannell J G, and Doggett W M. Survival after Starr Edwards aortic valve replacement. *Circulation* 44:1, 1971.
4. Barnhorst D A, Osman H A, Connolly D C, Pluth J R, Danielson G K, Wallace R B, and McGoon D C. Long term follow up of isolated replacement of the aortic and mitral valve with the Starr Edwards prosthesis. *Am J Cardiol* 35:228, 1975.
5. Munoz E, Gallardo J, Diaz Garrin J H, and Medina O. Influence of surgery on the natural history of rheumatic mitral and aortic valve disease. *Am J Cardiol* 35:234, 1975.
6. Gwalt J H, Covelli J W, Braunwald E, and Ross, J Jr. Left ventricular performance following correction of free aortic regurgitation. *Circulation* 42:773, 1970.
7. Smith H J, Neutze J M, Roche A H G, Agnew T M, and Barratt Boyes B G. The natural history of rheumatic aortic regurgitation and the indications for surgery. *Br Heart J* 38:147, 1976.
8. Bruce R A, Kusumi F, and Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 86:546, 1973.
9. Samson J, Slodov S, and Gruhn J C. Myocardial abscesses. *AM HEART J* 66:301, 1963.
10. Lerner P I, and Weinstein L. Infective endocarditis in the antibiotic era. *N Engl J Med* 274:388, 1966.
11. Laufer A. Human and experimental myocarditis. *Isr J Med Sci* 11:37, 1975.
12. Tomlinson C W, and Dhalla N S. Alterations in myocardial function during bacterial infective cardiomyopathy. *Am J Cardiol* 37:373, 1976.
13. Anderson W A, D. Pathology sixth edition. St Louis, 1971. The C V Mosby Company p 632.
14. Horstall, F L, and Tamm, I. Viral and Rickettsial infections of man fourth edition. Philadelphia 1965. J B Lippincott Company p 1144.
15. Weiss, E. Growth and physiology of rickettsiae. *Bacteriol Rev* 37:259, 1973.
16. Wilson H G, Neilson G H, Galea E G, Stafford G, and O'Brien M F. Q fever endocarditis in Queensland. *Circulation* 53:689, 1976.

Table II Left ventriculography data

| Case number | Ventriculogram  |                            | Coronary arteriogram  |                |
|-------------|---|----------------------------|-----------------------|----------------|
|             | Left ventricular wall motion                              | Location and degree of MVP | Location of spasm     | Fixed lesions  |
| 1           | Mild anterolateral hypokinesis                            | Mild AL and PM             | Left main diffuse RCA | Nil            |
| 2           | Mild apical hypokinesis Early diastolic relaxation        | Moderate PM                | Mid LAD               | Nil            |
| 3           | Mild generalized hypokinesis                              | None                       | Proximal RCA          | Nil            |
| 4           | Normal  | Mild middle and PM         | Proximal RCA          | Nil            |
| 5           | Inadequate long axis                                      | Mild PM                    | Proximal RCA          | Nil            |
| 6           | Normal  | Mild PM                    | Proximal RCA          | Nil            |
| 7           | Mild apical hypokinesis                                   | Mild PM                    | Proximal RCA          | Nil            |
| 8           | Inadequate long axis shortening Mild anterior hypokinesis | Mild PM                    | Proximal RCA          | Nil            |
| 9           | Normal  | Moderate AL middle and PM  | Proximal RCA          | 50% left main  |
| 10          | Mild anterior hypokinesis                                 | Moderate PM                | Proximal RCA          | 50% circumflex |

Eight of 10 patients had otherwise normal coronary arteries. One patient had a 50 per cent left main coronary artery lesion (Case 9) and one had a 50 per cent circumflex lesion (Case 10).

#### Discussion

Coronary artery spasm is associated with various disease entities including the syndrome of myocardial infarction with normal coronary arteries<sup>2,3</sup>, Prinzmetal's variant angina<sup>4</sup> and nitroglycerin withdrawal in munition workers.<sup>5</sup> Occasionally this condition occurs in patients with chest pain who have normal coronary arteries at angiography. In these cases the area of spasm is often within the coronary ostium suggesting that catheter trauma may be responsible for the induction of spasm in the proximal right or left main artery. However it is also conceivable that certain individuals may be predisposed to the development of catheter induced spasm because of an underlying abnormality of nervous or arterial smooth muscle activity.

Proximal coronary artery spasm is most often observed in patients with angina or chest pain syndromes and otherwise normal coronary arteries. In these individuals, spasm may not be simply a response to local catheter trauma but a sign of abnormal arterial smooth muscle tone. The occurrence of both spontaneous distal and catheter induced spasm in the same patient further suggests a pathophysiological basis for the latter event rather than a chance arteriographic curiosity.

The incidence of catheter induced spasm is quite low, varying between 0.26 per cent and 2.93 per cent in several studies.<sup>7-20</sup> It is difficult to determine the exact frequency of this phenomenon since pretreatment with nitrates, catheterization techniques and patient selection may influence the development of spasm in any one series. However the findings of coronary artery spasm in 1.34 per cent of patient in our study is consistent with the literature and attests to the infrequent occurrence of this event. In contrast mitral valve prolapse is more common and may be seen in 6 to 21 per cent of normal females.<sup>21,22</sup>

Although one cannot make an exact extrapolation of these data to our own series, the coincidental occurrence of mitral valve prolapse in nine of 10 patients with coronary artery spasm is indeed striking and raises the possibility of a common pathogenesis for the two conditions in some patients.

It is interesting that of the 10 patients with coronary artery spasm eight had a previous history of chest pain while only two patients had evidence of haemodynamically significant coronary artery disease. This observation agrees with previous reports in which coronary artery spasm whether catheter induced or spontaneous was frequently found in patients with angina or chest pain syndromes who had no fixed coronary arterial lesions implicating spasm as a cause of the pain.<sup>23,24</sup> The occurrence of both proximal and distal spasm in one of our patients complements



Table 1 Clinical and electrocardiographic features

| Case number | Age & sex | History                         | Physical examination | ECG findings   |
|-------------|-----------|---------------------------------|----------------------|--|
| 1           | 38 F      | Chest pain palpitations syncope | Systolic murmur      | Normal resting ST elevation with chest pain          |
| 2           | 33 F      | Chest pain                      | Mid-systolic click   | ST T changes (inferior and anterior)                 |
| 3           | 34 M      | Syncope palpitations            | Midsystolic click    | Normal   |
| 4           | 50 F      | Chest pain                      | Midsystolic click    | RBBB   |
| 5           | 46 M      | Chest pain dyspnea              | Nil                  | Normal   |
| 6           | 55 F      | Fatigue                         | Systolic murmur      | LVH & strain<br>ST T changes (inferior and anterior) |
| 7           | 42 F      | Chest pain                      | Nil                  | ST T changes (anterior)                              |
| 8           | 42 F      | Chest pain dyspnea              | Nil                  | ST T changes (anterior and inferior)                 |
| 9           | 39 F      | Chest pain                      | Nil                  | ST T changes (anterior)                              |
| 10          | 45 F      | Chest pain fatigue dyspnea      | Nil                  | ST T changes (inferior)                              |

the anterolateral commissural scallop produced an anterosuperior bulge, and prolapse of the posteromedial commissural scallop produced a posteroinferior bulge. The degree of mitral valve prolapse was assessed as 'mild,' 'moderate' or 'severe.'

The clinical findings and heart catheterization data were available for review in all 10 patients.

## Results

**Clinical and electrocardiographic features (Table I)** Of the 10 patients in this study eight were female. The average age was 42.5 years (range 33 to 55 years).

Notable symptoms included chest pain in eight patients, syncope in two, dyspnea in eight, palpitations in three, and fatigue in two. Of the two patients with syncopal episodes and palpitations one patient (Case 1) had documented recurrent ventricular tachyarrhythmias. In the other two patients with palpitations (Cases 3 and 8) no arrhythmias were documented.

Five patients had a systolic click or late systolic murmur on auscultation. One patient (Case 3) who had a systolic click with evidence of coronary artery spasm had no angiographically demonstrable mitral valve prolapse.

Seven patients had ECG abnormalities. These included ST-T changes over the anterior precordial leads in two, ST-T changes over the inferior leads in one, LVH and strain in one and complete right bundle branch block in one. Three patients had normal ECGs. One patient (Case 1) was subsequently found to have ST segment elevation coinciding with episodes of chest pain

suggesting Prinzmetal's variant angina. In this particular patient coronary artery spasm and mitral valve prolapse were demonstrated.

Two patients (Cases 1 and 9) underwent exercise ECG testing. Both patients had positive exercise tests.

**Left ventriculography (Table II)** Abnormalities of left ventricular wall motion were common in our series, occurring in seven of 10 patients. These findings are summarized in Table II and include mild anterolateral hypokinesis in one patient, mild apical hypokinesis in two, early diastolic anterior relaxation in one, inadequate long axis shortening in two, mild anterior hypokinesis in two and mild generalized hypokinesis in one. Three patients showed normal left ventricular wall motion.

Significantly, nine of 10 patients had evidence of mitral valve prolapse. This involved the posteromedial scallop in six patients, the anterolateral and posteromedial scallops in one (Fig 6), the middle and posteromedial scallops in one and the anterolateral middle and posteromedial scallops in one (Fig 3).

**Coronary arteriography (Table II)** There was documented coronary artery spasm in all 10 patients in this series. This involved the proximal right coronary artery in eight (Figs 1 and 2), the mid LAD in one, and the left main coronary artery in one (Figs 4 and 5). Of the 10 patients with coronary artery spasm eight patients had evidence of catheter induced spasm, one patient had spontaneous spasm and one patient had both spontaneous and catheter induced spasm.



Fig 3 Left ventriculogram of the same patient (Case 9) with evidence of prolapse involving the anterolateral (black arrow) middle (white arrow) and posteromedial scallop of the posterior mitral leaflet

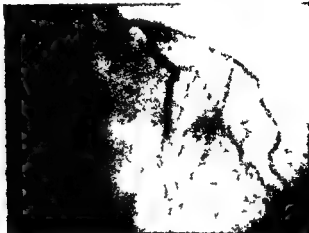


Fig 5 Repeat injection of the left coronary artery following nitroglycerin showing resolution of the previous spasm

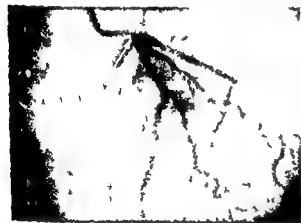


Fig 4 Selective coronary arteriogram showing spasm of the left main coronary artery (Case 1)



Fig 6 Left ventriculogram of the patient (Case 1) with evidence of prolapse involving the anterolateral scallop slightly (black arrow) but mainly the posteromedial scallop of the posterior mitral leaflet

may be mediated by alpha adrenergic receptors. Thus it is conceivable that phenylephrine may provoke chest pain by producing coronary artery spasm in susceptible patients. This observation is supported by a case report in which nitrate resistant coronary artery spasm was abolished by the alpha adrenergic receptor antagonist phenolamine.

In a recent report Chesler and co-workers<sup>2</sup> have observed four cases of mitral valve prolapse in which myocardial infarction occurred. Surprisingly, post infarction coronary arteriograms showed no evidence of organic coronary disease. These authors suspected that coronary artery spasm was the cause of the myocardial infarction although no evidence of spasm was demonstrated at angiography.

It appears that an ischemic mechanism may be a cause of chest pain in some patients with mitral valve prolapse. The occurrence of myocardial infarction without demonstrable coronary disease and the apparent association between the valvular abnormality and coronary artery spasm further suggest that transient vasoconstriction may well be the cause of the cardiac symptoms and complications in certain individuals with mitral valve prolapse.

#### Summary

Ten patients representing 1.34 per cent of those patients undergoing selective coronary arteriography were found to have unequivocal evidence of coronary artery spasm. This involved the proximal right coronary artery in eight



Fig 1 Selective coronary arteriogram showing spontaneous spasm of the proximal right coronary artery (Case 9)



Fig 2 Repeat injection of the right coronary artery after intravenous phentolamine showing almost complete resolution of the previous spasm

the earlier report of Chahine and associates<sup>9</sup> and suggests that catheter trauma may be a less important factor than has been previously believed.

In addition to pain, the symptoms of mitral valve prolapse have included dyspnea, fatigue, palpitations, presyncope and syncope.<sup>1</sup> Some observers have suggested that the perception of palpitations and faintness may be the result of atrial or ventricular arrhythmias.<sup>8</sup> Other have commented on the ischemic looking repolarization changes in the electrocardiogram.<sup>4</sup> There have also been reports of myocardial infarction with normal coronary arteries and sudden death<sup>11, 12</sup> in mitral valve prolapse patients.

The symptoms experienced by this patient population and the associated cardiac abnormalities suggest that an underlying ischemic mechanism may be operative in this condition. In support of this concept Natarajan and co-workers<sup>4</sup> have demonstrated that some patients with mitral valve prolapse show abnormalities of lactate metabolism presumably the result of myocardial ischemia.

Several postulates have been proposed to explain the pathogenesis of myocardial ischemia in mitral valve prolapse. Barlow and Bosman<sup>3</sup> initially speculated that compression of the circumflex artery by the dilated posterior leaflet could produce myocardial ischemia, but subsequent studies failed to demonstrate any distor-

tion of this vessel.<sup>13, 16</sup> Some observers have suggested a possible association between actual coronary artery disease and mitral valve prolapse to explain the cardiac symptoms, but this relationship appears to be fortuitous and of no etiologic importance.<sup>3</sup>

The possibility that an ischemic focus in the papillary muscle may be produced by increased papillary muscle stress resulting from the billowing scallops has also been considered.<sup>14</sup> In support of this concept Le Winter and colleagues<sup>15</sup> have shown that intravenous phenylephrine may induce chest pain in patients with mitral valve prolapse. These authors have suggested that phenylephrine, by increasing systolic arterial pressure, may produce a discrepancy between myocardial oxygen supply and demand in the papillary muscle under increased tension and thus lead to chest pain. Their data further suggest that chest discomfort associated with mitral valve prolapse is organic in nature and probably not entirely functional as proposed by others.

There is however an alternative mechanism for phenylephrine induced chest pain in mitral valve prolapse patients. This agent is also a potent alpha adrenergic receptor agonist and has been shown to produce coronary artery constriction *in vivo* and *in vitro*.<sup>16</sup> Yasue and associates<sup>17, 18</sup> have suggested that severe spasm of large coronary arteries in Prinzmetal's angina



Fig 3 Left ventriculogram of the same patient (Case 9) with evidence of prolapse involving the anterolateral (black arrow) middle (white arrow) and posteromedial scallops of the posterior mitral leaflet

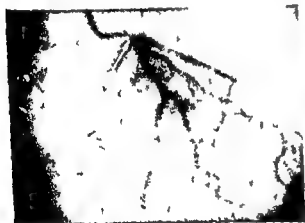


Fig 4 Selective coronary arteriogram showing spasm of the left main coronary artery (Case 1)

may be mediated by alpha adrenergic receptors. Thus it is conceivable that phenylephrine may provoke chest pain by producing coronary artery spasm in susceptible patients. This observation is supported by a case report in which nitrate resistant coronary artery spasm was abolished by the alpha adrenergic receptor antagonist phenolamine.

In a recent report Chesler and co workers<sup>7</sup> have observed four cases of mitral valve prolapse in which myocardial infarction occurred. Surprisingly, post infarction coronary arteriograms showed no evidence of organic coronary disease. These authors suspected that coronary artery spasm was the cause of the myocardial infarction, although no evidence of spasm was demonstrated at angiography.



Fig 5 Repeat injection of the left coronary artery following nitroglycerin showing resolution of the previous spasm



Fig 6 Left ventriculogram of the patient (Case 1) with evidence of prolapse involving the anterolateral scallop slightly (black arrow) but mainly the posteromedial scallop of the posterior mitral leaflet

It appears that an ischemic mechanism may be a cause of chest pain in some patients with mitral valve prolapse. The occurrence of myocardial infarction without demonstrable coronary disease and the apparent association between the valvular abnormality and coronary artery spasm further suggest that transient vasoconstriction may well be the cause of the cardiac symptoms and complications in certain individuals with mitral valve prolapse.

### Summary

Ten patients representing 13.4 per cent of those patients undergoing selective coronary arteriography were found to have unequivocal evidence of coronary artery spasm. This involved the proximal right coronary artery in eight



Fig 1 Selective coronary arteriogram showing spontaneous spasm of the proximal right coronary artery (Case 9)



Fig 2 Repeat injection of the right coronary artery after intravenous phenolamine showing almost complete resolution of the previous spasm

the earlier report of Chahine and associates<sup>9</sup> and suggests that catheter trauma may be a less important factor than has been previously believed.

In addition to pain the symptoms of mitral valve prolapse have included dyspnea, fatigue, palpitations, presyncope and syncope.<sup>1</sup> Some observers have suggested that the perception of palpitations and faintness may be the result of atrial or ventricular arrhythmias.<sup>9</sup> Other have commented on the ischemic looking repolarization changes in the electrocardiogram.<sup>4</sup> There have also been reports of myocardial infarction with normal coronary arteries and sudden death<sup>11, 13, 15</sup> in mitral valve prolapse patients.

The symptoms experienced by this patient population and the associated cardiac abnormalities suggest that an underlying ischemic mechanism may be operative in this condition. In support of this concept Natarajan and co-workers<sup>9</sup> have demonstrated that some patients with mitral valve prolapse show abnormalities of lactate metabolism presumably the result of myocardial ischemia.

Several postulates have been proposed to explain the pathogenesis of myocardial ischemia in mitral valve prolapse. Barlow and Bosman<sup>21</sup> initially speculated that compression of the circumflex artery by the dilated posterior leaflet could produce myocardial ischemia but subsequent studies failed to demonstrate any distor-

tion of this vessel.<sup>6, 9, 10</sup> Some observers have suggested a possible association between actual coronary artery disease and mitral valve prolapse to explain the cardiac symptoms but this relationship appears to be fortuitous and of no etiologic importance.<sup>5</sup>

The possibility that an ischemic focus in the papillary muscle may be produced by increased papillary muscle stress resulting from the billowing scallops has also been considered.<sup>22</sup> In support of this concept, Le Winter and colleagues<sup>23</sup> have shown that intravenous phenylephrine may induce chest pain in patients with mitral valve prolapse. These authors have suggested that phenylephrine by increasing systolic arterial pressure may produce a discrepancy between myocardial oxygen supply and demand in the papillary muscle under increased tension and thus lead to chest pain. Their data further suggest that chest discomfort associated with mitral valve prolapse is organic in nature and probably not entirely functional as proposed by others.

There is, however, an alternative mechanism for phenylephrine induced chest pain in mitral valve prolapse patients. This agent is also a potent alpha adrenergic receptor agonist and has been shown to produce coronary artery constriction *in vivo* and *in vitro*.<sup>24</sup> Yasue and associates<sup>25</sup> have suggested that severe spasm of large coronary arteries in Prinzmetal's angina

## Electrode position effects on Frank lead electrocardiograms

Alan S Berson Ph D  
W Kenneth Haisty MD  
Hubert V Pipberger MD  
Washington D C

In electrocardiography the electrical potentials obtained from precordial electrodes depend to a great extent on the precise location of these electrodes. One of the goals of every proposed lead system is to specify as precisely as possible the location of electrodes relative to well defined anatomic landmarks. In doing this it is anticipated that the variability of electrocardiographic potentials unrelated to variations in the electrical activity of the heart will be reduced.

In the original description of his lead system Frank<sup>1</sup> specified that the location of all chest and back electrodes be at the level of the fifth interspace at the sternal border for sitting or standing subjects. Subsequently Langner and co workers<sup>2</sup> proposed that the fourth interspace be used when applied to recumbent subjects. This recommendation resulted from the better agreement they obtained when comparing the Frank system to Schmitt and Simonson's SVEC III system.<sup>3</sup> Since then some laboratories have used the fourth interspace and others have continued to use the fifth interspace for Frank electrode locations.

Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure. The typical recording equipment includes a patient

cable having all leads necessary for applying electrodes of both systems at the same time. Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded. To reduce the number of necessary electrodes many investigators have used the location for standard lead V<sub>4</sub> and Frank lead A interchangeably. Additionally the electrode for standard lead V<sub>4</sub> has become acceptable by some as Frank electrode C.

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1. In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown. In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border. It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V<sub>4</sub> and A electrode positions in individuals.

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V<sub>4</sub> for C. Results of electrocardiographic measurements are reported for four different variations of electrode placement.

### Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system. These versions will be referred to as Systems 1, 2, 3, and 4.

System 1 Electrodes A, C, E, I, and M applied according to Frank with all electrodes placed at

From the Veterans Administration Research Center for Cardiovascular Data Processing, Veterans Administration Hospital and the Departments of Clinical Engineering and Medicine, The George Washington University, Washington, D C.

Supported by the Medical Research Service of the Veterans Administration and by Research Grant HL 15047 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland.

Received for publication November 2, 1976.

Accepted for publication January 8, 1977.

Reprint requests: H V Pipberger MD, VA Hospital (151B) 50 Irving St., NW, Washington, DC 20472.

patients, the mid left anterior descending branch in one, and the left main coronary artery in one. Eight of these 10 patients had otherwise normal coronary arteries.

Of these 10 patients with coronary artery spasm, nine had evidence of mitral valve prolapse. This involved the posteromedial scallop in six patients, the anterolateral and posteromedial scallops in one, the middle and posteromedial scallops in one, and the anterolateral, middle, and posteromedial scallops in one.

These data suggest an association between coronary artery spasm and mitral valve prolapse. Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain, arrhythmias, electrocardiographic abnormalities, and sudden death, that have already been described in some patients with mitral valve prolapse.

The authors gratefully acknowledge the assistance of Drs E D Wigle, H Rakowski, and M B McLaughlin for their interest and advice in the preparation of this paper.

#### REFERENCES

- Wigle ED, Rakowski H, Ranganathan N and Silver M D Mitral valve prolapse. *Annu Rev Med* volume 27 1976
- Chesler E, Matson RE, Lakier J H, Pocock W A, Obel I W P and Barlow J B Acute myocardial infarction with normal coronary arteries. *Circulation* 54 203 1976
- Barlow J H and Pocock W A The problem of non-ejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am HEART J* 90 636 1975
- Pocock W A and Barlow J B Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. *Am J Med* 51 731 1971
- Jeremias R M Etiology of the mitral valve prolapse click syndrome. *Am J Cardiol* 38 110 1975
- Nutter D O, Wickliffe C, Gilbert C A, Moody C and King E B The pathophysiology of idiopathic mitral valve prolapse. *Circulation* 52 297 1975
- Scamporrino C, Yang S S, Maranhao V, Goldberg H and Gooch A S Left ventricular abnormalities in prolapsed mitral leaflet syndrome. *Circulation* 48 287 1973
- Gooch A S, Virencio F, Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. *Am J Cardiol* 29 611 1972
- Lobstein H P, Horwitz L D, Curry G C and Mullins C B Electrocardiographic abnormalities and coronary arteriograms in mitral click murmur syndrome. *N Engl J Med* 289 127 1973
- Jeremias R M Mitral valve prolapse click syndrome. *Progr Cardiovasc Dis* 15 623 1973
- Trent J K, Adelman A G, Wigle F D and Silver M D Morphology of a prolapsed mitral valve leaflet. *Am HEART J* 79 539 1970
- Ranganathan N, Silver M D, Robinson T, Kostuk W J, Felderhof C H, Patt N L, Wilson J H, L. Wigle E D Angiographic morphologic correlation in patients with severe mitral regurgitation due to prolapse of the posterior mitral leaflet. *Circulation* 48 514 1973
- Ranganathan N, Lam J H C, Wigle E D and Silver M D Morphology of the human mitral valve leaflet. *Circulation* 41 459 1970
- Khan A H and Haywood L J Myocardial infarction in nine patients with radiologically patent coronary arteries. *N Engl J Med* 291 477 1974
- Oliva P B, Potts D E and Pluss R G Coronary arterial spasm in Prinzmetal's angina. *N Engl J Med* 288 745 1973
- Lange R L, Reid M S, Tresch D D, Keeler M H, Bernhard V M and Coughlin G Nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure. *Circulation* 46 666 1972
- Demany M, Tambe A and Zimmerman H Coronary arterial spasm. *Dis Chest* 53 714 1968
- O'Reilly R, Spellberg R and Jung T Recognition of proximal right coronary artery spasm during coronary arteriography. *Radiology* 95 305 1970
- Lavine P, Kimbiris D and Linhart J Coronary artery spasm during selective coronary arteriography: a review of 8 years' experience. (Abstr.) *Circulation* 48(Suppl. IV) 89 1973
- Chahine R A, Raizner A F, Ishimon T, Luchs R J and McIntosh H D The incidence and clinical implications of coronary artery spasm. *Circulation* 52 92 1975
- Markiewicz W, Stoner J, London E, Hunt S A and Popp R Mitral valve prolapse in 100 presumably healthy young females. *Circulation* 53 464 1976
- Procacci P M, Savran S V, Schreiner S L and Bryson A L Prevalence of clinical mitral valve prolapse in 1169 young women. *N Engl J Med* 294 1086 1976
- Barlow J H and Bosman C A Aneurysmal protrusion of the posterior leaflet of the mitral valve. *Am HEART J* 71 1066 1966
- Shappell D S, Marshall C F, Brown R E and Bruce T A Sudden death and the familial occurrence of midsystolic click late systolic murmur syndrome. *Circulation* 48 1128 1973
- Hancock E W and Cohn K L The syndrome associated with midsystolic click and late systolic murmur. *Am J Med* 41 183 1966
- Natarajan G, Nakayama F, Kahn D, Yazkaner S, Sahabzada W, Khawaja F and Goldbert H Myocardial metabolic studies in prolapsing mitral leaflet syndrome. *Circulation* 52 1105 1975
- LeWinter M M, Hoffman J R, Shell W E, Karlner J S and O'Rourke R A Phenylephrine induced atypical chest pain in patients with prolapsing mitral valve leaflets. *Am J Cardiol* 34 12 1974
- Bayer B, Mentz P and Forster W Characterization of the adrenoceptors in coronary arteries of pigs. *Eur J Pharmacol* 29 58 1974
- Yasue H, Touyama M, Kata H, Tanaka S and Akiyama F Prinzmetal's variant form of angina as a manifestation of alpha adrenergic receptor mediated coronary artery spasm. *Am HEART J* 91 148 1976
- Yasue H, Touyama M, Shimamoto M, Tanaka S and Akiyama F Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation* 50 534 1974
- Levene D L and Myers M G Catheter induced coronary spasm. *Can Med Assoc J* 111 64 1974

## Electrode position effects on Frank lead electrocardiograms

Alan S Berson Ph D  
W Kenneth Haisty MD  
Hubert V Pipberger MD  
Washington D C

In electrocardiography the electrical potentials obtained from precordial electrodes depend to a great extent on the precise location of these electrodes. One of the goals of every proposed lead system is to specify as precisely as possible the location of electrodes relative to well defined anatomic landmarks. In doing this it is anticipated that the variability of electrocardiographic potentials unrelated to variations in the electrical activity of the heart will be reduced.

In the original description of his lead system Frank<sup>1</sup> specified that the location of all chest and back electrodes be at the level of the fifth interspace at the sternal border for sitting or standing subjects. Subsequently Langner and co workers<sup>2</sup> proposed that the fourth interspace be used when applied to recumbent subjects. This recommendation resulted from the better agreement they obtained when comparing the Frank system to Schmitt and Simonson's SVEC III system.<sup>3</sup> Since then some laboratories have used the fourth interspace and others have continued to use the fifth interspace for Frank electrode locations.

Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure. The typical recording equipment includes a patient

cable having all leads necessary for applying electrodes of both systems at the same time. Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded. To reduce the number of necessary electrodes many investigators have used the location for standard lead V<sub>4</sub> and Frank lead A interchangeably. Additionally the electrode for standard lead V has become acceptable by some as Frank electrode C.

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1. In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown. In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border. It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V<sub>4</sub> and A electrode positions in individual cases.

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V<sub>4</sub> for C. Results of electrocardiographic measurements are reported for four different variations of electrode placement.

### Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system. These versions will be referred to as Systems 1, 2, 3, and 4.

System 1 Electrodes A, C, E, I, and M applied according to Frank with all electrodes placed at

From the Veterans Administration Research Center for Cardiovascular Data Processing, Veterans Administration Hospital, and the Departments of Clinical Engineering and Medicine, The George Washington University, Washington, D C.

Supported by the Medical Research Service of the Veterans Administration and by Research Grant HL 15047 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland.

Received for publication May 3, 1976.

Accepted for publication Jan 6, 1977.

Reprint requests: H V Pipberger MD, VA Hospital (1513), 50 Irving St., NW, Washington, DC 20422.



patients, the mid left anterior descending branch in one, and the left main coronary artery in one. Eight of these 10 patients had otherwise normal coronary arteries.

Of these 10 patients with coronary artery spasm, nine had evidence of mitral valve prolapse. This involved the posteromedial scallop in six patients, the anterolateral and posteromedial scallops in one, the middle and posteromedial scallops in one, and the anterolateral, middle, and posteromedial scallops in one.

These data suggest an association between coronary artery spasm and mitral valve prolapse. Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain, arrhythmias, electrocardiographic abnormalities, and sudden death, that have already been described in some patients with mitral valve prolapse.

The authors gratefully acknowledge the assistance of Drs E D Wigle, H Rakowski, and M B McLaughlin for their interest and advice in the preparation of this paper.

#### REFERENCES

- Wigle E D, Rakowski H, Ranganathan N and Silver M D. Mitral valve prolapse. *Annu Rev Med* volume 27 1976.
- Chesler E, Mattson R E, Laher J B, Pocock W A, Obel I W P and Barlow J B. Acute myocardial infarction with normal coronary arteries. *Circulation* 54 203 1976.
- Barlow J B and Pocock W A. The problem of nonejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am Heart J* 90 636 1975.
- Pocock W A and Barlow J B. Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. *Am J Med* 51 731 1971.
- Jeresaty R M. Etiology of the mitral valve prolapse click syndrome. *Am J Cardiol* 36 110 1975.
- Nutter D O, Wickliffe C, Gilbert C A, Moody C and King S B. The pathophysiology of idiopathic mitral valve prolapse. *Circulation* 52 297 1975.
- Scamporrino G, Yang S S, Maranhao V, Goldberg H and Gooch A S. Left ventricular abnormalities in prolapsed mitral leaflet syndrome. *Circulation* 48 287 1973.
- Gooch A S, Vicencio F, Maranhao V and Goldberg H. Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. *Am J Cardiol* 29 611 1972.
- Lobtein H P, Horwitz L D, Curry G C and Mullins C B. Electrocardiographic abnormalities and coronary arteriograms in mitral click murmur syndrome. *N Engl J Med* 289 127 1973.
- Jeresaty R M. Mitral valve prolapse click syndrome. *Progr Cardiovasc Dis* 15 623 1973.
- Trent J K, Adelman A G, Wigle E D and Silver M D. Morphology of a prolapsed mitral valve leaflet. *Am Heart J* 79 539 1970.
- Ranganathan N, Silver M D, Robinson T, Kostuk W J, Felderhof C H, Patt N L, Wilson J A and Wigle E D. Angiographic morphologic correlation in patients with severe mitral regurgitation due to prolapse of the posterior mitral leaflet. *Circulation* 48 514 1973.
- Ranganathan N, Lam J H C, Wigle E D and Silver M D. Morphology of the human mitral valve leaflets. *Circulation* 41 459 1970.
- Khan A H and Haywood L J. Myocardial infarction in nine patients with radiologically patent coronary arteries. *N Engl J Med* 291 477 1974.
- Oliva P B, Potts D E and Pluss R G. Coronary arterial spasm in Prinzmetal's angina. *N Engl J Med* 288 745 1973.
- Lange R L, Reid M S, Tresch D D, Keelan M H, Bernhard V M and Coolidge G. Nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure. *Circulation* 46 668 1972.
- Demany M, Tambe A and Zimmerman H. Coronary arterial spasm. *Dis Chest* 53 714 1968.
- O'Reilly R, Spellberg R and King T. Recognition of proximal right coronary artery spasm during coronary arteriography. *Radiology* 95 30 1970.
- Lavine P, Kimbiris D and Linhart J. Coronary artery spasm during selective coronary arteriography: a review of 8 years experience (Abstract). *Circulation* 48 (suppl. IV) IV 89 1973.
- Chahine R A, Razner A E, Ishimori T, Luchi R J and McIntosh H D. The incidence and clinical implications of coronary artery spasm. *Circulation* 52 93 1975.
- Markiewicz W, Stoner J, London E, Hunt S A and Popp R. Mitral valve prolapse in 100 presumably healthy young females. *Circulation* 53 464 1976.
- Procacci P M, Savran S V, Schreier S L, and Bryson A L. Prevalence of clinical mitral valve prolapse in 1169 young women. *N Engl J Med* 294 1086 1976.
- Barlow J B and Bosman C A. Aneurysmal protrusion of the posterior leaflet of the mitral valve. *Am Heart J* 71 166 1966.
- Shappell D S, Marshall C E, Brown R E and Bruce T A. Sudden death and the familial occurrence of midsystolic click late systolic murmur syndrome. *Circulation* 48 1128 1973.
- Hancock E W and Cohn K L. The syndrome associated with midsystolic click and late systolic murmur. *Am J Med* 41 183 1966.
- Natarajan G, Nakayama F K, Kahn D, Yazkanlar S, Sahabzada W, Khawaja F and Goldberg H. Myocardial metabolic studies in prolapsing mitral leaflet syndrome. *Circulation* 52 1105 1975.
- LeWinter M M, Hoffman J R, Shell W E, Karlner J S and O'Rourke D A. Phenylephrine induced atypical chest pain in patients with prolapsing mitral valve leaflets. *Am J Cardiol* 34 12 1974.
- Bayer B, Mentz P and Forster W. Characterization of the adrenoceptors in coronary arteries of pigs. *Eur J Pharmacol* 29 58 1974.
- Yasue H, Toyama M, Kata H, Tanaka S and Akiyama F. Prinzmetal's variant form of angina as a manifestation of alpha adrenergic receptor mediated coronary artery spasm. *Am Heart J* 91 148 1976.
- Yasue H, Toyama M, Shimamoto M, Tanaka S and Akiyama F. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation* 50 534 1974.
- Levene D L and Myers M G. Catheter induced coronary spasm. *Can Med Assoc J* 111 647 1974.

# Experimental and laboratory reports

## Electrode position effects on Frank lead electrocardiograms

Alan S Berson Ph D  
W Kenneth Haisty MD  
Hubert V Pipberger MD  
Washington ■ C

In electrocardiography the electrical potentials obtained from precordial electrodes depend to a great extent on the precise location of these electrodes. One of the goals of every proposed lead system is to specify as precisely as possible the location of electrodes relative to well defined anatomic landmarks. In doing this it is anticipated that the variability of electrocardiographic potentials unrelated to variations in the electrical activity of the heart will be reduced.

In the original description of his lead system Frank<sup>1</sup> specified that the location of all chest and back electrodes be at the level of the fifth intercostal space at the sternal border for sitting or standing subjects. Subsequently Langner and co workers<sup>2</sup> proposed that the fourth interspace be used when applied to recumbent subjects. This recommendation resulted from the better agreement they obtained when comparing the Frank system to Schmitt and Simonson's SVEC III system.<sup>3</sup> Since then some laboratories have used the fourth interspace and others have continued to use the fifth interspace for Frank electrode locations.

Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure. The typical recording equipment includes a patient

cable having all leads necessary for applying electrodes of both systems at the same time. Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded. To reduce the number of necessary electrodes many investigators have used the location for standard lead V<sub>4</sub> and Frank lead A interchangeably. Additionally the electrode for standard lead V<sub>4</sub> has become acceptable by some as Frank electrode C.

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1. In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown. In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border. It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V<sub>4</sub> and A electrode positions in individuals.

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V<sub>4</sub> for C. Results of electrocardiographic measurements are reported for four different variations of electrode placement.

### Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system. These versions will be referred to as Systems 1, 2, III, and 4.

System 1 Electrodes A, C, E, I, and M applied according to Frank with all electrodes placed at

From the Veterans Administration Research Center for Cardiovascular Data Processing, Veterans Administration Hospital, and the Departments of Clinical Engineering and Medicine, The George Washington University, Washington, D C.

Supported by the Medical Research Service of the Veterans Administration, and by Research Grant HL 15047 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland.

Received for publication on Nov 3, 1977.

Accepted for publication Jan 6, 1978.

Reprint requests: H V Pipberger, MD, VA Hospital (151S), 50 Irving St., NW, Washington, D C 20422.

patients, the mid left anterior descending branch in one, and the left main coronary artery in one. Eight of these 10 patients had otherwise normal coronary arteries.

Of these 10 patients with coronary artery spasm, nine had evidence of mitral valve prolapse. This involved the posteromedial scallop in six patients, the anterolateral and posteromedial scallops in one, the middle and posteromedial scallops in one, and the anterolateral middle, and posteromedial scallops in one.

These data suggest an association between coronary artery spasm and mitral valve prolapse. Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain, arrhythmias, electrocardiographic abnormalities, and sudden death that have already been described in some patients with mitral valve prolapse.

The authors gratefully acknowledge the assistance of Drs E D Wigle, H Rakowski, and M B McLaughlin for their interest and advice in the preparation of this paper.

#### REFERENCES

- Wigle E D, Rakowski H, Ranganathan N and Silver M D Mitral valve prolapse. *Annu Rev Med* volume 27 1976
- Chesler E, Matison R E, Lakier J B, Pocock W A, Obel I W P and Barlow J B Acute myocardial infarction with normal coronary arteries. *Circulation* 54 203 1976
- Barlow J B and Pocock W A The problem of nonjunction systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am Heart J* 90 636 1975
- Pocock W A and Barlow J B Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. *Am J Med* 51 731 1971
- Jeresaty R M Etiology of the mitral valve prolapse click syndrome. *Am J Cardiol* 36 110 1975
- Nutter D O, Wickliffe C, Gilbert C A, Moody C and King S B The pathophysiology of idiopathic mitral valve prolapse. *Circulation* 52 297 1975
- Scamporrino G, Yang S S, Maranhao V, Goldberg H and Gooch A S Left ventricular abnormalities in prolapsed mitral leaflet syndrome. *Circulation* 48 287 1973
- Gooch A S, Vicencio F, Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. *Am J Cardiol* 29 611 1972
- Lobstein H P, Horwitz L D, Curry G C and Mullins C B Electrocardiographic abnormalities and coronary arteriograms in mitral click murmur syndrome. *N Engl J Med* 289 127 1973
- Jeresaty R M Mitral valve prolapse click syndrome. *Progr Cardiovasc Dis* 15 623 1973
- Trent J K, Adelman A G, Wigle E D and Silver M D Morphology of a prolapsed mitral valve leaflet. *Am Heart J* 79 539 1970
- Ranganathan N, Silver M D, Robinson T, Kostuk W J, Felderhof C H, Patt N L, Wilson J K and Wigle E D Angiographic morphologic correlation in patients with severe mitral regurgitation due to prolapse of the posterior mitral leaflet. *Circulation* 48 514 1973
- Ranganathan N, Lam J H C, Wigle E D and Silver M D Morphology of the human mitral valve leaflets. *Circulation* 41 459 1970
- Khan A H and Haywood L J Myocardial infarction in nine patients with radiologically patent coronary arteries. *N Engl J Med* 291 47 1974
- Oliva P B, Potts D E and Fluss R G Coronary arterial spasm in Prinzmetal's angina. *N Engl J Med* 288 745 1973
- Lange K L, Reid M S, Tresch D D, Keelan V H, Bernhard V M and Coolidge G Nonatherosclerotic ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure. *Circulation* 46 668 1972
- Demany M, Tambe A and Zimmerman H Coronary arterial spasm. *Dis Chest* 53 714 1968
- O'Reilly H, Spellberg H and King T Recognition of proximal right coronary artery spasm during coronary arteriography. *Radiology* 95 306 1970
- Lavine P, Kimbire D and Linhart J Coronary artery spasm during selective coronary arteriography: a review of 8 years experience (Abstr). *Circulation* 48 (suppl IV) IV 89 1973
- Chahine R A, Razner A E, Ishimon T, Luch R J and McIntosh H D The incidence and clinical implications of coronary artery spasm. *Circulation* 52 971 1975
- Markiewicz W, Stoner J, London E, Hunt S A and Popp R Mitral valve prolapse in 100 presumably healthy young females. *Circulation* 53 464 1976
- Procacci P M, Savran S V, Schreiner S L and Bryson A L Prevalence of clinical mitral valve prolapse in 1169 young women. *N Engl J Med* 294 1086 1976
- Barlow J B and Bosman C A Aneurysmal protrusion of the posterior leaflet of the mitral valve. *Am Heart J* 71 166 1966
- Shappel D S, Marshall C E, Brown H E and Bruce T A Sudden death and the familial occurrence of mid-systolic click late systolic murmur syndrome. *Circulation* 48 1128 1973
- Hancock E W and Cohn K L The syndrome associated with mid-systolic click and late systolic murmur. *Am J Med* 41 183 1966
- Natarajan G, Nakayama F K, Kahn D, Laksanfar S, Sahabzada W, Khawaja F and Goldbert H Myocardial metabolic studies in prolapsing mitral leaflet syndrome. *Circulation* 52 1105 1975
- LeWinter M M, Hoffman J H, Shell W E, Karliner J S and O'Rourke R A Phenylephrine induced atypical chest pain in patients with prolapsing mitral valve leaflets. *Am J Cardiol* 34 12 1974
- Bayer E, Mentz P and Forster W Characterization of the adrenoceptors in coronary arteries of pigs. *Eur J Pharmacol* 29 58 1974
- Yasue H, Toyama M, Kata H, Tanaka S, and Akiyama F Prinzmetal's variant form of angina as a manifestation of alpha adrenergic receptor mediated coronary artery spasm. *Am Heart J* 91 144 1976
- Yasue H, Toyama M, Shumamoto M, Tanaka S and Akiyama F Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation* 50 534 1974
- Levene D L and Myers M G Catheter induced coronary spasm. *Can Med Assoc J* 111 647 1974

Table I Mean standard deviation and 96 percentile range for selected amplitudes and durations for 149 subjects

|                      | Fifth interspace |         |            |          |         |            | Fourth interspace |         |            |          |         |            |
|----------------------|------------------|---------|------------|----------|---------|------------|-------------------|---------|------------|----------|---------|------------|
|                      | System 1         |         |            | System 2 |         |            | System 3          |         |            | System 4 |         |            |
|                      | Mean             | Std dev | 96% range  | Mean     | Std dev | 96% range  | Mean              | Std dev | 96% range  | Mean     | Std dev | 96% range  |
| Q <sub>r</sub> †     | ~0.43            |         | 0 to ~19   | ~0.35    |         | 0 to ~14   | ~0.47             |         | 0 to ~19   | ~0.41    |         | 0 to ~17   |
| R <sub>r</sub> †     | 1.13             | .56     |            | 1.04     | .53     |            | 1.18              | .51     |            | 1.13     | .56     |            |
| S                    | ~12              |         | 0 to ~45   | ~13      |         | 0 to ~50   | ~12               |         | 0 to ~45   | ~13      |         | 0 to ~49   |
| T                    | .00              | .18     |            | .01      | .18     |            | .08               | .20     |            | .05      | .19     |            |
| P max                | .049             |         | 0 to .095  | .046     |         | 0 to .087  | .055              |         | 0 to .10   | .055     |         | 0 to .10   |
| Q                    | ~33              |         | 0 to ~80   | ~32      |         | 0 to ~82   | ~30               |         | 0 to ~80   | ~32      |         | 0 to ~80   |
| R <sub>r</sub>       | .84              | .49     |            | .93      | .54     |            | .89               | .50     |            | .83      | .55     |            |
| T                    | ~18              |         | 0 to ~44   | ~20      |         | 0 to ~47   | ~20               |         | 0 to ~80   | ~20      |         | 0 to ~42   |
| P                    | .027             |         | 0 to 0.9   | .078     |         | 0 to .083  | .031              |         | 0 to .075  | .030     |         | 0 to .080  |
| Y                    | ~0.38            |         | 0 to ~0.85 | ~0.40    |         | 0 to ~0.87 | ~0.35             |         | 0 to ~0.73 | ~0.38    |         | 0 to ~0.75 |
| QRS Spat. Max        | 1.55             | .58     |            | 1.57     | .58     |            | 1.59              | .60     |            | 1.59     | .59     |            |
| P Spat. Max          | 1                |         | 0 to .11   | 12       |         | 0 to 21    | 18                |         | 0 to 19    | 12       |         | 0 to .20   |
| T Spat. Max          | .09              |         | 0 to .58   | .31      |         | 0 to .61   | .32               |         | 0 to .57   | .37      |         | 0 to .60   |
| Q <sub>r</sub> Dur ‡ | .80              |         | 0 to 23    | .70      |         | 0 to 21    | .80               |         | 0 to 24    | .80      |         | 0 to 23    |
| Q <sub>r</sub> Dur   | 31.0             |         | 0 to 57    | 30.0     |         | 0 to 51    | 28.0              |         | 0 to 48    | 29.0     |         | 0 to 50    |

System 1 = Frank System, fifth interspace; System 2 = Frank system, fifth interspace, except V used in place of Frank electrode III; System 3 = Frank system, fourth interspace; System 4 = Frank system, fourth interspace, except V used in place of Frank electrode C.

†Amplitudes are in millivolts.

‡Durations are in msec.

§Ranges are for  $r$  measurements with skewed distributions.

**Amplitudes and durations** Means standard deviation and 96 percentile ranges for each amplitude and duration measurement for each electrode system are listed in Table I. The large overlap in measurement ranges from one system to another is undoubtedly in part due to the inhomogeneity of the sample, i.e. normal and abnormal groups included together. For those measurements which are normally and nearly normally distributed the  $t$  statistic showed no significant difference at the 0.05 level between the means of system 1 and each of the other systems.

For many subjects individual differences in amplitudes were not uncommon. This kind of information is summarized in Table II in which only differences exceeding both 0.10 millivolt and 10 per cent of System 1 values were considered. This table clearly shows that differences are least when Systems 1 and 2 are compared. When V is substituted for C the trend toward decreasing R and increasing R is clear. This trend remained the same even when all electrodes were shifted to the fourth interspace as may be seen when comparing Systems 1 and 4. For a level shift upward without substituting V for C both R

and R increased in approximately twice as many cases as they decreased. T amplitude changes occurred less frequently than those in QRS. System 3 showed these changes most but even then such changes occurred in less than 10 per cent of the records.

**Orientations** Angular mean values and mean angular deviations shown in Table III were calculated according to the methods suggested by Batschelet.<sup>6</sup> A mean vector for all subjects is determined by obtaining mean values of sines and cosines. The polar angle of the mean vector is called the mean angle. A measure of dispersion called the mean angular deviation is calculated as

$$S = \sqrt{2(1-r)}$$

where  $r$  is the mean angle with both  $r$  and  $S$  in radians.

The mean elevation angle remained essentially unchanged for all four electrode systems. Azimuth mean angles remained almost unchanged for Systems 2, 3 and 4, all being about 8 degrees different from that of System 1. However, mean angular deviation was close to 40 degrees for all four systems so that differences in the mean angle are not clearly significant.

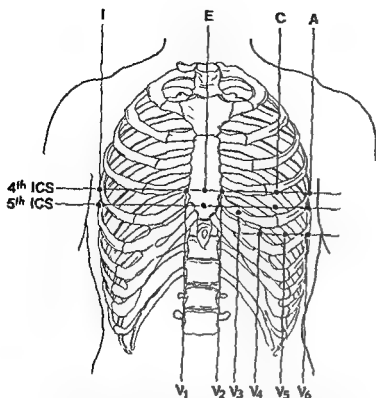


Fig 1 Electrode locations for standard precordial and Frank electrodes at the level of the fourth and fifth intercostal spaces relative to the rib cage. Electrode C location must be determined using an angular measurement not shown here although it generally falls to the left of V. Biologic variations in rib cage curvature may cause large discrepancies between V and A locations in individual cases.

the level of the fifth interspace at the sternal border

**System 2** Identical to System 1 except that standard precordial lead  $V_4$  is used in place of electrode C

**System 3** Identical to System 1 except that the level of all electrodes is at the fourth interspace at the sternal border

**System 4** Identical to System 3 except that standard precordial lead  $V_4$  is used in place of electrode C

The clinical diagnoses of the 149 subjects were determined by history and physical examination data without knowledge of electrocardiographic information. These diagnoses were as follows: 66—Normal, 36—Coronary Artery Disease (CAD), 20—Hypertensive Cardiovascular Disease (HCVD), nine—Valvular Heart Disease, nine—Pulmonary Disease, eight—HCVD and CAD and one—Valvular and Pulmonary Disease.

Eleven patient leads were used in addition to two leg leads and a head lead which enabled placement of all electrodes before recording started. Four sequential orthogonal electrocar-

diograms, corresponding to each of the four systems were obtained for each patient using a four position, manually operated switch. The switch allowed the same Frank resistor network and three preamplifiers to be used for each recording. Each recording consisted of a calibration signal plus 20 seconds of electrocardiographic signal on three channels of FM magnetic tape.

Becton Dickinson type 7901 silver/silverchloride electrodes with 11 mm diameter were used. Electrode wells were filled with electrode paste before application. Buffer amplifiers provided no less than 50 megohms input impedance for each patient input lead. Electrode positions were marked with patients supine.

The data were processed utilizing the Veterans Administration electrocardiographic analysis program<sup>3</sup> using a Control Data Corporation 300 computer. Details of analog to digital conversion, wave recognition and measurements have been published previously,<sup>4</sup> and therefore only a brief summary will be presented here.

The three electrocardiographic leads are each digitized at 2 msec intervals for 10 seconds after being filtered with a 200 Hz, low pass filter. Wave recognition consists of identifying the beginning and end of P and QRS and the end of T using spatial velocity as the main criterion. Measurements of amplitudes and durations are made on each cardiac cycle from which waves are identified. Ectopic beats are discarded and average values of measurements of the remaining beats are then used.

## Results

To make comparisons among the four systems for each subject System 1 was selected as the baseline and results obtained from each of the other three systems were compared to it.

The following sets of measurements were selected for comparison of results:

**Amplitudes** Q, R, S, T, P, Q<sub>R</sub>, R<sub>S</sub>, T<sub>P</sub>, QRS<sub>m</sub> (maximum spatial QRS magnitude), P<sub>m</sub> (maximum spatial P magnitude) and T<sub>m</sub> (maximum spatial T magnitude).

**Durations** Q and Q<sub>R</sub>

**Orientations** QRS<sub>K</sub> (elevation angle for QRS<sub>m</sub>) and QRS<sub>A</sub> (azimuth angle for QRS<sub>m</sub>).

No y lead measurements were examined because the principal electrodes (F and H) contributing to the y lead remained unchanged for all four systems.

Table 1 Mean, standard deviation and 96 percentile range for selected amplitudes and durations for 149 subjects

|               | Fifth interspace |         |            |          |         |            | Fourth interspace |         |            |          |         |            |
|---------------|------------------|---------|------------|----------|---------|------------|-------------------|---------|------------|----------|---------|------------|
|               | System 1         |         |            | System 2 |         |            | System 3          |         |            | System 4 |         |            |
|               | Mean             | Std dev | 96% range  | Mean     | Std dev | 96% range  | Mean              | Std dev | 96% range  | Mean     | Std dev | 96% range  |
| Q,†           | -.043            |         | 0 to -.19  | -.035    |         | 0 to -.14  | -.047             |         | 0 to -.11  | -.041    |         | 0 to -.17  |
| R             | 1.13             | .58     |            | 1.04     | .53     |            | 1.18              | .58     |            | 1.13     | .56     |            |
| S             | -.12             |         | 0 to -.45  | -.13     |         | 0 to -.50  | -.12              |         | 0 to -.45  | -.13     |         | 0 to -.49  |
| T             | .070             | .18     |            | .061     | .18     |            | .082              | .20     |            | .085     | .19     |            |
| P max.        | .049             |         | 0 to .095  | .046     |         | 0 to .087  | .055              |         | 0 to .10   | .055     |         | 0 to .10   |
| Q             | -.33             |         | 0 to -.80  | -.33     |         | 0 to -.82  | -.30              |         | 0 to -.80  | -.32     |         | 0 to -.80  |
| R             | .84              | .49     |            | .93      | .54     |            | .89               | .50     |            | .93      | .55     |            |
| T             | -.18             |         | 0 to -.44  | -.20     |         | 0 to -.47  | -.20              |         | 0 to -.50  | -.20     |         | 0 to -.49  |
| P             | .027             |         | 0 to .079  | .078     |         | 0 to .089  | .031              |         | 0 to .075  | .030     |         | 0 to .080  |
| T             | -.038            |         | 0 to -.085 | -.040    |         | 0 to -.092 | -.035             |         | 0 to -.073 | -.038    |         | 0 to -.075 |
| QRS Spat. Max | 1.55             | .58     |            | 1.57     | .58     |            | 1.59              | .60     |            | 1.59     | .58     |            |
| I Spat. Max   | .12              |         | 0 to .11   | .12      |         | 0 to .21   | .18               |         | 0 to .19   | .18      |         | 0 to .20   |
| T Spat. Max   | .29              |         | 0 to .50   | .31      |         | 0 to .61   | .32               |         | 0 to .57   | .37      |         | 0 to .60   |
| Q, Dur.‡      | .80              |         | 0 to .93   | .70      |         | 0 to .21   | .80               |         | 0 to .25   | .80      |         | 0 to .23   |
| Q, Dur        | .310             |         | 0 to .67   | .300     |         | 0 to .51   | .280              |         | 0 to .48   | .290     |         | 0 to .50   |

System 1 = Frank System fifth interspace System 2 = Frank system fifth interspace except V used in place of Frank electrode C System 3 = Frank system, fourth interspace System 4 = Frank system fourth interspace except V used in place of Frank electrode C

†Amplitudes are in millivolts

‡Durations are in msec.

§Ranges are given for measurements with skewed distribution.

**Amplitudes and durations** Means standard deviations and 96 percentile ranges for each amplitude and duration measurement for each electrode system are listed in Table I. The large overlap in measurement ranges from one system to another is undoubtedly in part due to the inhomogeneity of the sample i.e. normal and abnormal groups included together. For those measurements which are normally and nearly normally distributed the *t* statistic showed no significant difference at the 0.05 level between the means of System 1 and each of the other systems.

For many subjects individual differences in amplitudes were not uncommon. This kind of information is summarized in Table II in which only differences exceeding both 0.10 millivolt and 10 per cent of System 1 values were considered. This table clearly shows that differences are least when Systems 1 and 2 are compared. When V is substituted for C the trend toward decreasing R and increasing R is clear. This trend remained the same even when all electrodes were shifted to the fourth interspace as may be seen when comparing Systems 1 and 4. For a level shift upward without substituting V for C both R

and R increased in approximately twice as many cases as they decreased. T amplitude changes occurred less frequently than those in QRS. System 3 showed these changes most but even then such changes occurred in less than 10 per cent of the records.

**Orientations** Angular mean values and mean angular deviations shown in Table III were calculated according to the methods suggested by Batschelet.<sup>4</sup> A mean vector for all subjects is determined by obtaining mean values of sines and cosines. The polar angle of the mean vector is called the mean angle. A measure of dispersion called the mean angular deviation is calculated as

$$S = \sqrt{2(1-r)}$$

where *r* is the mean angle with both *r* and *S* in radians.

The mean elevation angle remained essentially unchanged for all four electrode systems. Azimuth mean angles remained almost unchanged for Systems 2, 3 and 4 all being about 8 degrees different from that of System 1. However mean angular deviation was close to 40 degrees for all four systems so that differences in the mean angle are not clearly significant.

**Table II** Number of cases with significant amplitude changes using System 1 as reference

|                           | System 2 | System 3 | System 4 |
|---------------------------|----------|----------|----------|
| Amplitude change† in      | 61 (41)* | 104 (70) | 101 (68) |
| R or QRS <sub>m</sub>     |          |          |          |
| R decrease                | 36 (24)  | 22 (15)  | 27 (18)  |
| R increase                | 4 (3)    | 38 (26)  | 19 (13)  |
| R <sub>s</sub> decrease   | 5 (3)    | 25 (17)  | 16 (11)  |
| R increase                | 39 (26)  | 46 (31)  | 61 (41)  |
| QRS <sub>m</sub> decrease | 10 (7)   | 20 (13)  | 13 (9)   |
| QRS <sub>m</sub> increase | 9 (6)    | 34 (23)  | 25 (17)  |
| Amplitude change in       | 0        | 14 (9)   | 6 (4)    |
| T or T <sub>m</sub>       |          |          |          |
| T decrease                | 0        | 2 (1)    | 1 (5)    |
| T increase                | 0        | 2 (1)    | 1 (5)    |
| T decrease                | 0        | 10 (7)   | 6 (4)    |
| T increase                | 0        | 1 (5)    | 1 (5)    |
| T <sub>m</sub> decrease   | 0        | 1 (5)    | 0        |
| T <sub>m</sub> increase   | 0        | 7 (5)    | 3 (2)    |
| No change in QRS or       | 82 (55)  | 34 (23)  | 35 (23)  |
| T amplitudes              |          |          |          |

Percentages of 149 subjects are shown in parentheses.

†Amplitude change is calculated as the difference between an amplitude value in Systems 2, 3, or 4 with respect to its value in System 1. The change is significant if it is both greater than 0.10 millivolt and at least 10 per cent of the value in System 1.

**Limits of measurements** Most electrocardiographic analysis programs depend on limits of one or more measurements for diagnostic classification. The effect of electrode level change on normal limits was observed for 16 common measurements. The results, shown in Table IV, indicate the number of records for which measurements changed from normal to abnormal or vice versa. The normal limits used are those developed using the Veterans Administration data base of 510 well documented cases<sup>8</sup> developed for Frank leads applied at the fourth intercostal space.

**Electrode locations—C versus V<sub>4</sub>** For each subject, measurements were made of the distances between C and V<sub>4</sub> electrodes. Ranges and means of distances are presented in Table V. The location of C was invariably to the left of V<sub>4</sub>.

## Discussion

The effects of electrode misplacement have been studied previously,<sup>9,10</sup> so it is not surprising to find that the different versions of the Frank system studied in this report also produce electrocardiographic changes. Generally greater differences are produced as additional electrodes are

misplaced. However, the C electrode is usually the single most sensitive electrode in this respect. In Table II, note that 41 per cent of the records had significant amplitude changes in R, R<sub>s</sub>, or QRS<sub>m</sub> (greater than both 0.1 millivolt and 10 per cent of System 1 values) when V<sub>4</sub> was substituted for C. When all chest electrodes were moved to the fourth interspace, this number was increased to 70 per cent.

The data in Table II for R<sub>s</sub>, R<sub>m</sub>, and QRS<sub>m</sub> were tested for significance of differences using the Wilcoxon matched pairs signed ranks test.<sup>11</sup> This test is useful for making judgements about the magnitude and direction of differences within pairs. Application of this test demonstrated that the trends for decreasing R<sub>s</sub> and increasing R from Systems 1 to 2 were highly significant ( $p = 0.0003$ ). On the other hand, QRS<sub>m</sub> changes were not significant, i.e., no trend toward increasing or decreasing magnitude was evident.

When comparing Systems 1 to 3, the trend for R increase was also significant ( $p = 0.02$ ). As noted from the  $p$  values, this trend was not so strong as the R<sub>s</sub> decreasing trend for Systems 1 to 2. However, the total number of records for which R<sub>s</sub> changes occurred was much greater for System 3 (60 opposed to 40). Trends for R and QRS<sub>m</sub> increases were significant at  $p = 0.06$  and  $p = 0.05$  levels, respectively, between Systems 1 and 3.

Some general conclusions one can draw from these data are that:

1. With V<sub>4</sub> substituted for C, about 40 per cent of the records are affected by amplitude changes in R, R<sub>s</sub>, or QRS<sub>m</sub>, 25 to 30 per cent have R<sub>s</sub> or R<sub>m</sub> changes, and about 20 per cent have QRS<sub>m</sub> changes. In those records with changes, eight to nine times as many have lower R and higher R<sub>s</sub> values than vice versa, and QRS<sub>m</sub> values are equally likely to increase or decrease.

2. With all electrodes shifted from the fifth to the fourth interspace, R, R<sub>s</sub>, and QRS<sub>m</sub> changes occur in about 70 per cent of the cases. R<sub>s</sub> is affected in about 40 per cent, R<sub>m</sub> in about 50 per cent, and QRS<sub>m</sub> in about 35 per cent of the records. In those records with changes, R, R<sub>s</sub>, and QRS<sub>m</sub> increase in about two thirds and decrease in about one third of the cases. However, as will be noted later in this section, it is difficult to predict increases or decreases in amplitudes when electrode level is shifted from the fifth to the fourth interspace.

In an effort to determine if electrocardiographic changes were correlated with disease groups

Table III Means and deviations for azimuth and elevation angles for 149 subjects for four electrode systems

| Angular function | Fifth interspace |                      |                  |                      | Fourth interspace |                      |                  |                      |
|------------------|------------------|----------------------|------------------|----------------------|-------------------|----------------------|------------------|----------------------|
|                  | System 1 (C)     |                      | System 2 (V)     |                      | System 3 (C)      |                      | System 4 (V)     |                      |
|                  | Mean angle (deg) | Mean angle dev (deg) | Mean angle (deg) | Mean angle dev (deg) | Mean angle (deg)  | Mean angle dev (deg) | Mean angle (deg) | Mean angle dev (deg) |
| Elevation†       | 19.7             | 19.1                 | 40.0             | 19.2                 | 18.7              | 19.1                 | 19.3             | 18.4                 |
| Azimuth‡         | 17.5             | 40.0                 | 25.9             | 41.2                 | 25.7              | 37.5                 | 25.3             | 39.2                 |

Angular definitions are according to American Heart Association recommendations.

†Azimuth angle is in the horizontal plane and is positive for posterior angles.

‡Elevation angle is positive for inferior angles.

normal subjects, HCVD patients and pulmonary disease patients were studied separately. Amplitude changes for R, R<sub>s</sub> and QRS<sub>m</sub> for these three groups are presented in Table VI.

For both the 66 normal subjects and the 20 patients with HCVD amplitude changes with electrode shifts followed the same patterns as for all 149 subjects considered together.

For the nine pulmonary disease patients some what different results were obtained. For System 3 R, R<sub>s</sub> and QRS<sub>m</sub> all tended to decrease in contrast to the normal subjects and HCVD patients. This finding is consistent with the lower diaphragm and heart locations usually found in pulmonary disease patients as contrasted with normals. To verify this observation additional patients in this group would have been useful.

In a study by Draper and co-workers<sup>9</sup> normal limits for many commonly used measurements were determined for the Frank system with electrodes applied at the level of the fourth intercostal space. An appropriate question would be: If these normal limits are applied, how often would key measurements used for diagnostic classification change significantly when electrodes are shifted to the level of the fifth intercostal space? Table IV provides some answers. For example, one record having an R value outside of normal limits when recording at the level of the fifth intercostal space was recorded with a normal R value at the level of the fourth intercostal space. The reverse was true for seven other subjects. This finding could have affected diagnosis for left ventricular hypertrophy (LVH). Similarly, R and (R/S) changed in 17 and 6 subjects respectively, which could have affected diagnosis for LVH, right ventricular hypertrophy (RVH) or chronic obstructive pulmonary disease.

Table IV Changes of selected amplitude amplitude ratio and angular measurements for 149 subjects. The number of subjects in which measured values changed from within normal limits to outside of normal limits or vice versa as electrode level is shifted from the fifth to the fourth intercostal space.

|                       | System 1 vs 3 |            |
|-----------------------|---------------|------------|
|                       | Abn to nor    | Nor to abn |
| Maximum QRS           | 1             | 2          |
| Maximum QRS           | 6             | 10         |
| Maximum QRS           | 1             | 6          |
| Q                     | 8             | 10         |
| R                     | 1             | 7          |
| S                     | 4             | 7          |
| Q                     | 5             | 9          |
| R                     | 9             | 8          |
| J                     | 3             | 4          |
| J                     | 13            | ■          |
| QRS <sub>m</sub>      | 0             | 0          |
| (Q/R)                 | 0             | 0          |
| (R/S)                 | 4             | 2          |
| (Q/R)                 | 0             | ■          |
| Maximum QRS elevation | 0             | 4          |
| Maximum QRS azimuth   | 21            | 3          |

Normal limits are determined from the Veterans Administration data base of 510 cases recorded with electrodes at the fourth intercostal space level.

Table V Electrode distances in centimeters between V<sub>4</sub> and C in fourth and fifth intercostal spaces for 149 subjects

|   | Mean | Range   |
|---|------|---------|
| V to C, Fifth intercostal space                           | 3.5  | 1.5-6.0 |
| V to C, Fourth intercostal space                          | 5.3  | 3.0-7.5 |
| C, Fifth intercostal space to C, Fourth intercostal space | 2.7  | 2.0-4.0 |



**Table II** Number of cases with significant amplitude changes using System 1 as reference

|                                  | System 2 | System 3 | System 4 |
|----------------------------------|----------|----------|----------|
| Amplitude change† in             | 61 (41)* | 104 (70) | 101 (68) |
| R decrease                       | 36 (24)  | 22 (15)  | 27 (18)  |
| R increase                       | 4 (3)    | 38 (26)  | 19 (13)  |
| R decrease                       | 5 (3)    | 25 (17)  | 16 (11)  |
| R increase                       | 39 (26)  | 46 (31)  | 61 (41)  |
| QRS <sub>m</sub> decrease        | 10 (7)   | 20 (13)  | 13 (9)   |
| QRS <sub>m</sub> increase        | 9 (6)    | 34 (23)  | 25 (17)  |
| Amplitude change in              | 0        | 14 (9)   | 6 (4)    |
| T decrease                       | 0        | 2 (1)    | 1 (5)    |
| T increase                       | 0        | 2 (1)    | 1 (5)    |
| T decrease                       | 0        | 10 (7)   | 6 (4)    |
| T increase                       | 0        | 1 (5)    | 1 (5)    |
| T <sub>m</sub> decrease          | 0        | 1 (5)    | 0        |
| T <sub>m</sub> increase          | 0        | 7 (5)    | 3 (2)    |
| No change in QRS or T amplitudes | 82 (55)  | 34 (23)  | 35 (23)  |

Percentages of 149 subjects are shown in parentheses  
 †Amplitude change is calculated as the difference between an amplitude value in Systems 2, 3, or 4 with respect to its value in System 1. The change is significant if it is both greater than 0.10 millivolt and at least 10 per cent of the value in System 1.

**Limits of measurements** Most electrocardiographic analysis programs depend on limits of one or more measurements for diagnostic classification. The effect of electrode level change on normal limits was observed for 16 common measurements. The results, shown in Table IV, indicate the number of records for which measurements changed from normal to abnormal or vice versa. The normal limits used are those developed using the Veterans Administration data base of 510 well documented cases<sup>8</sup> developed for Frank leads applied at the fourth intercostal space.

**Electrode locations—C versus V<sub>1</sub>** For each subject measurements were made of the distances between C and V<sub>1</sub> electrodes. Ranges and means of distances are presented in Table V. The location of C was invariably to the left of V<sub>1</sub>.

## Discussion

The effects of electrode misplacement have been studied previously,<sup>9,11</sup> so it is not surprising to find that the different versions of the Frank system studied in this report also produce electrocardiographic changes. Generally, greater differences are produced as additional electrodes are

misplaced. However, the C electrode is usually the single most sensitive electrode in this respect. In Table II, note that 41 per cent of the records had significant amplitude changes in R, R<sub>s</sub>, or QRS<sub>m</sub> (greater than both 0.1 millivolt and 10 per cent of System 1 values) when V<sub>1</sub> was substituted for C. When all chest electrodes were moved to the fourth interspace, this number was increased to 70 per cent.

The data in Table II for R, R<sub>s</sub>, and QRS<sub>m</sub> were tested for significance of differences using the Wilcoxon matched pairs signed ranks test.<sup>12</sup> This test is useful for making judgements about the magnitude and direction of differences within pairs. Application of this test demonstrated that the trends for decreasing R<sub>s</sub> and increasing R<sub>s</sub> from Systems 1 to 2 were highly significant ( $p = 0.0003$ ). On the other hand QRS<sub>m</sub> changes were not significant, i.e. no trend toward increasing or decreasing magnitude was evident.

When comparing Systems 1 to 3, the trend for R<sub>s</sub> increase was also significant ( $p = 0.02$ ). As noted from the  $p$  values, this trend was not so strong as the R<sub>s</sub> decreasing trend for Systems 1 to 2. However, the total number of records for which R<sub>s</sub> changes occurred was much greater for System 3 (60 opposed to 40). Trends for R and QRS<sub>m</sub> increases were significant at  $p = 0.06$  and  $p = 0.05$  levels respectively, between Systems 1 and 3.

Some general conclusions one can draw from these data are that:

1. With V<sub>1</sub> substituted for C about 40 per cent of the records are affected by amplitude changes in R, R<sub>s</sub>, or QRS<sub>m</sub>. 25 to 30 per cent have R or R<sub>s</sub> changes, and about 20 per cent have QRS<sub>m</sub> changes. In those records with changes eight to nine times as many have lower R and higher R<sub>s</sub> values than vice versa and QRS<sub>m</sub> values are equally likely to increase or decrease.

2. With all electrodes shifted from the fifth to the fourth interspace, R, R<sub>s</sub>, and QRS<sub>m</sub> changes occur in about 70 per cent of the cases, R<sub>s</sub> is affected in about 40 per cent, R in about 50 per cent, and QRS<sub>m</sub> in about 35 per cent of the records. In those records with changes R, R<sub>s</sub> and QRS<sub>m</sub> increase in about two thirds and decrease in about one third of the cases. However as will be noted later in this section it is difficult to predict increases or decreases in amplitudes when electrode level is shifted from the fifth to the fourth interspace.

In an effort to determine if electrocardiographic changes were correlated with disease groups

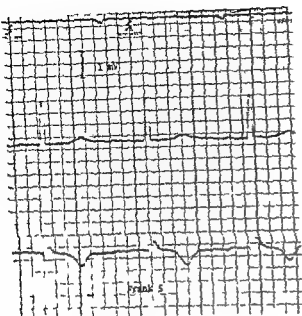


Fig 2A Frank lead recording with electrodes at the level of the fifth intercostal space. Only x and z leads shown

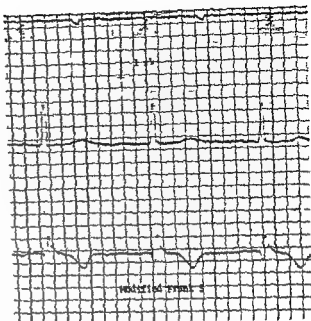


Fig 2B Frank lead recording of same patient with V substituted for C electrode. Note R increase from about 0.4 to 0.6 millivolt and II decrease from about 1.8 to 1.6 millivolt

that the bipolar precordial leads can provide a lead vector almost parallel to the y axis when they are symmetrically located above and below the source (dipole) location." No quantitative figures were given for amplitude differences between the fourth and fifth intercostal space recordings.

In the present study no attempt was made to determine which of the two electrode levels was optimum for the Frank lead system. To do so would require ideally determination of the electrical center of the heart. There is an indirect relationship between the level of the electrical center and the level at which maximum QRS amplitudes are found. In torso model experiments conducted by Frank " the critical horizontal level (maximum bulge in image space) usually corresponded to this level for maximum QRS amplitudes.

The differences in results between this study and that of Ritsema van Eck are difficult to reconcile but neither technique for estimating the critical horizontal level is sufficiently accurate for the determination of the optimum level in any specific case. A final resolution of this question may not be possible for real subjects and, at the least, will require a study using more exacting techniques.

The results of the present study stand out in

sharp contradiction to those reported recently by Riekkinen and Rautaharju.<sup>1</sup> Using the same definitions for significant changes these authors found that R, R<sub>s</sub> and QRS<sub>m</sub> decreased in 39, 45 and 40 per cent of their records (144 patients) when electrodes were shifted from the fifth to the fourth intercostal spaces in the supine position. Increased values were found in less than 1 per cent of the records. These figures contrast sharply with results shown in Table II in which decreases in R, R<sub>s</sub> and QRS<sub>m</sub> were observed in 15, 17 and 13 per cent of the records and increases in 26, 31, and 23 per cent of the records. It is of interest to note that the percentages of records in which any changes occurred regardless of direction were remarkably similar for both studies.

There may be at least one explanation for these discrepancies that is related to the subject's position during electrode application. In Table II of Riekkinen and Rautaharju<sup>1</sup> data are presented for electrocardiographic measurement changes with shift in electrode level for both supine and sitting subjects. Although amplitudes decreased consistently in both cases when electrode level was shifted from the fifth to the fourth intercostal space the percentages of records in which this occurred was considerably less for the sitting subjects. For example QRS<sub>m</sub> decreased in 40.3 per cent for supine and in only 19.4 per cent for sitting.

**Table VI** Number of cases having significant amplitude changes for 66 normal subjects, 20 subjects with hypertensive cardiovascular disease (HCVD), and 9 subjects with pulmonary disease\*

|   | System 2 |         |            | System 3 |         |            | System 4 |         |            |
|---|----------|---------|------------|----------|---------|------------|----------|---------|------------|
|   | Normals  | HCVD    | Pulm. dis. | Normals  | HCVD    | Pulm. dis. | Normals  | HCVD    | Pulm. dis. |
| Amplitude changes<br>—R, R <sub>i</sub> , or QRS <sub>m</sub> | 26 (39)† | 11 (30) | 4 (44)     | 48 (73)  | 13 (65) | 5 (55)     | 49 (74)  | 13 (65) | 4 (44)     |
| R <sub>i</sub> decrease                                       | 15 (23)  | 2 (10)  | 1 (11)     | 9 (14)   | 2 (10)  | 2 (22)     | 8 (12)   | 1 (5)   | 2 (22)     |
| R increase  | 1 (2)    | 0       | 1 (11)     | 21 (32)  | 7 (35)  | 0          | 9 (14)   | 4 (20)  | 1 (11)     |
| R decrease  | 2 (3)    | 0       | 1 (11)     | 5 (8)    | 1 (5)   | 3 (33)     | 7 (11)   | 1 (5)   | 2 (22)     |
| R increase  | 9 (14)   | 3 (15)  | 1 (11)     | 23 (35)  | 7 (35)  | 1 (11)     | 26 (39)  | 8 (40)  | 1 (11)     |
| QRS <sub>m</sub> decrease                                     | 7 (11)   | 0       | 1 (11)     | 6 (9)    | 2 (10)  | 2 (22)     | 6 (9)    | 2 (10)  | 0          |
| QRS <sub>m</sub> increase                                     | 0        | 0       | 2 (22)     | 16 (24)  | 6 (30)  | 0          | 8 (12)   | 4 (20)  | 0          |
| No change in QRS or T AMP                                     | 36 (55)  | 14 (70) | 5 (55)     | 10 (15)  | 6 (30)  | 4 (44)     | 12 (18)  | 6 (30)  | 3 (33)     |

\*See footnote to Table II for definition of significant changes

†Percentages are shown in parentheses

**Table VII** Number of records with significant changes for two studies in this laboratory (studies 1 and 2) and one reported by Riekkinen and Rautaharju (study 3)<sup>19</sup>

| Measurement*           | Study 1<br>(149<br>records) | Study 2<br>(137<br>records) | Study 3<br>(144<br>records) |
|------------------------|-----------------------------|-----------------------------|-----------------------------|
| <b>R</b>               |                             |                             |                             |
| 4th ICS > 5th ICS      | 38                          | 31                          | 1                           |
| 4th ICS = 5th ICS      | 89                          | 68                          | 87                          |
| 4th ICS < 5th ICS      | 22                          | 38                          | 66                          |
| <b>R<sub>i</sub></b>   |                             |                             |                             |
| 4th ICS > 5th ICS      | 46                          | 36                          | 6                           |
| 4th ICS = 5th ICS      | 78                          | 60                          | 73                          |
| 4th ICS < 5th ICS      | 11                          | 41                          | 65                          |
| <b>QRS<sub>m</sub></b> |                             |                             |                             |
| 4th ICS > 5th ICS      | 34                          | 20                          | 1                           |
| 4th ICS = 5th ICS      | 95                          | 78                          | 85                          |
| 4th ICS < 5th ICS      | 20                          | 39                          | 58                          |

All recordings are for the supine position with electrodes in the fourth and fifth intercostal spaces (ICS)

Whether or not a particular record is misclassified obviously depends on a combination of measurement changes, which was not specifically determined in this study. However, it seems clear that a change in diagnosis is likely to occur as a result of applying the same voltage level criteria to both fourth and fifth intercostal level recordings for the same subject.

Figs 2 and 3 show the typical way in which lead voltages are affected by electrode position. In Fig 2, lead voltages for the Frank fifth interspace level are compared when V<sub>1</sub> is used instead of C

Lead x is noticeably decreased and lead z increased in amplitude when using V<sub>1</sub>. In Fig 3 fourth and fifth level Frank leads are compared. For this patient, both x and z lead voltages are higher for the fifth interspace.

In previous studies comparing fourth and fifth intercostal level recordings by Gau and Smith<sup>15</sup> (15 subjects) and by Slany<sup>14</sup> (50 patients), the authors found no statistical differences in Frank lead electrocardiographic amplitudes. Our own findings are similar, but there is disagreement in the conclusions which were drawn. Whereas Gau and Smith<sup>15</sup> conclude that a simple transformation could be used when comparing data in both electrode configurations, individual variations found in our own study would not support this conclusion. Furthermore as reported by Horan and associates<sup>16</sup> among others, no general transformation can be applied to electrocardiograms to convert amplitudes or orientations from one system to another because of the wide range of biologic variations. The conclusion by Slany<sup>14</sup> that results obtained with either electrode configuration were interchangeable is also inappropriate in view of the large amplitude differences detected in many individual cases, e.g., 70 per cent of records affected (Table II).

Rutsema van Eck,<sup>18</sup> in a study of electrode levels, concluded that x and z lead electrodes should be located below the fourth intercostal space. His conclusions were based on a cross correlation technique for determination of the optimum Frank electrode level in 44 normal subjects. This technique relies on the assumption

Table VIII Comparison of means and ranges of amplitude changes among several studies For each subject the absolute value of the difference between the measurement in system 1 and that in systems 2 3 or 4 is determined The mean is then calculated for 149 subjects

| systems 2 3 or 4 is determined. The mean is then calculated for the |                       |              |                       |              |                       |              |               |                     |     |           |     |                          |     |
|---|-----------------------|--------------|-----------------------|--------------|-----------------------|--------------|---------------|---------------------|-----|-----------|-----|--------------------------|-----|
| Measurement   | System 2<br>5th ICS-V |              | System 3<br>4th ICS-C |              | System 4<br>4th ICS-V |              | Beat to Beat† | Day to Day normals‡ |     |           |     | Day to Day<br>abnormals§ |     |
|   | Mean                  | 96%<br>range | Mean                  | 96%<br>range | Mean                  | 96%<br>range |               | Mean                |     | 96% Range |     |                          |     |
|   | m                     | unn          | m                     | unn          | m                     | unn          |               | m                   | unn | m         | unn |                          |     |
| II  | 11                    | .37          | 15                    | .39          | 11                    | .76          | 08            | 09                  | 14  | .31       | .61 | 09                       | .36 |
| R <sub>1</sub>  | 10                    | .41          | 14                    | .37          | 15                    | .44          | 05            | 05                  | 09  | .30       | .35 | 08                       | .40 |
| QRS <sub>m</sub>  | 08                    | .25          | 15                    | .37          | 12                    | .37          | 06            | .07                 | 11  | .21       | .50 | 10                       | .35 |

All values are in millivolts

†D is from Fischmann et al.

‡Data are from Willem et al.

§Data are from Kim et al.

Abbreviations: ICS = intercostal space; SD = standard deviations; m = marked; unn = unmarked

Riekkinen and Rautaharju (their Table II) \* The most striking features appear to be that (1) all three studies produce qualitatively different results and (2) the two studies from this laboratory are more nearly similar to each other than either is to the study of Riekkinen and Rautaharju.<sup>14</sup> To test these suppositions further the complex chi-square procedure was applied for each measurement to two groups at a time, e.g. study 1 versus study 2 study 1 versus study 3 and study 2 versus study 3. The null hypothesis used was that no difference exists between the pair of studies under test. In fact for II and R the chi-square value was not significant at the 0.05 level when comparing both studies from this laboratory. Chi-square values were highly significant ( $p < 0.0001$ ) when comparing either of these studies to that of Riekkinen and Rautaharju.<sup>14</sup> For QRS<sub>m</sub> the chi-square value was borderline for  $p = 0.05$  when comparing both studies from this laboratory. Again when comparing either study with that of Riekkinen and Rautaharju,<sup>14</sup> chi-square values were highly significant with  $p < 0.0001$  in both instances. We must conclude then, that the data from both studies in this laboratory were not statistically dissimilar and that both sets of data were statistically different from those of Riekkinen and Rautaharju.<sup>14</sup> It is apparent also from the data of Table VII that it generally is not possible to predict in which way amplitudes will change when electrode level is displaced from the fifth to the fourth intercostal space.

It may be of interest to compare the variations in electrocardiographic measurements that were

found in this study to those found in studies of beat to beat and day to day variations. Fischmann and co workers<sup>15</sup> studied beat to beat and observer variation in a series of 58 Frank lead records. They reported results for a variety of amplitude and duration measurements. For II, R and QRS<sub>m</sub> they calculated values of 0.8, 0.5 and 0.8 millivolts respectively representing mean differences plus two standard deviations of the differences using nine beats from each record. These values are significantly lower than those obtained in this study (Table VIII).

Two of the recent studies on day to day variation of the Frank lead electrocardiogram were reported by Willem and co workers<sup>16</sup> for a series of 20 normal subjects and by Kim and co workers<sup>17</sup> for a series of 20 patients. 19 of them with hypertensive cardiovascular disease. Data from these studies for R, II and QRS<sub>m</sub> are also shown in Table VIII. As a general observation it may be concluded from these data that variations caused by recording with Systems 2, 3 or 4 as compared with System 1 are of the same order of magnitude as day to day variations. This does not mean however that consistency with electrode locations in the Frank system is of little importance. In the present study no day to day variations were included. Thus the values shown in Table VIII reflect only those errors caused by intentionally displacing electrode locations. If day to day variations are considered in addition to this errors will most likely be compounded although they will not generally be additive algebraically.

There appears to be no conclusive evidence for

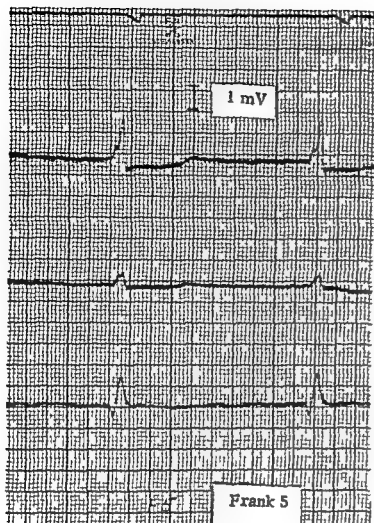


Fig 3A Frank lead recording with electrodes at the level of the fifth intercostal space

subjects. Since electrodes were not repositioned between supine and sitting positions, these differences in results were probably caused by skin shifts relative to the ribs.

It is well known that the skin tends to shift upwards when an individual moves from standing or sitting to a supine position. In locating a chest electrode at the level of the fifth interspace for a standing subject, for example, experiences in our own laboratory have indicated that it will usually be at or closer to the fourth interspace with the subject supine. In the study by Riekkinen and Rautaharju<sup>19</sup> fourth and fifth interspace electrode positions were marked with the subjects standing. In the supine position these levels were probably closer to the third and fourth interspaces, in which case the reduced electrocardiographic amplitudes with the higher electrode levels are more understandable. In the sitting position their results still are in contradiction, although slightly less so, to those in the present study in which electrode positions were marked with patients supine. We can only surmise then

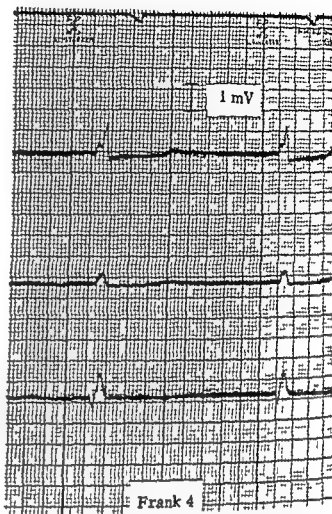


Fig 3B Frank lead recording of same patient with electrodes at the level of the fourth intercostal space. Note R decrease from about 1.1 to 0.9 millivolt and R decrease from about 1.6 to 1.2 millivolt.

that this difference in the subjects' posture during marking of electrodes is responsible for the differences in results between the two studies. There is, of course, also the possibility that these differences occurred by chance, but the fact that a similar number of subjects was used in both studies makes this seem unlikely.

Incidentally, the increase in electrocardiographic amplitudes noted by Riekkinen and Rautaharju<sup>19</sup> when subjects move from supine to sitting positions has also been observed in a recent study by Shapiro and colleagues.<sup>20</sup> These authors have attributed this mainly to skin shifts (and thereby electrode shifts) relative to heart position.

The discrepancies in results between those of Riekkinen and Rautaharju<sup>19</sup> and our own prompted a second study conducted in our laboratory with a new group of 137 male adults. Table VII lists results of this study for R, R<sub>s</sub>, and QRS, alongside results of the first study and those of

- in Vectorcardiography edited by I Hoffman and R C  
Taymor Philadelphia 1966 p 38 J B Lippincott  
Company
- Borun, III R. Variability of electrocardiographic data  
recorded with orthogonal leads, *AM HEART J* 76 62  
1968
- Berson A S Gamboa R Naval J A and Pipberger H  
V Differences caused by changes in electrode positions  
in two corrected orthogonal lead systems *J Electrocar  
diol* 3 29 1970
- Wilcoxon F Individual comparisons by ranking meth  
ods *Biometrics Bulletin* 1 80 1945
- Gau G T and Smith R E The effect of electrode  
position on a modified Frank electrovectorcardiographic  
lead system, *Mayo Clin Proc* 46 536 1971
- Slany J Zur Elektrodenanlage beim Frankischen Ableit  
ungssystem *Z. Kreislaufforsch* 61 1105 1972
- Horan L G Flowers N C., and Brody D A The  
interchangeability of vectorcardiographic systems, *AM  
HEART J* 70 365 1965
- Rutsema van Eck H J Anatomical level of Y and Z  
electrodes in the Frank VCG lead system *J Electrocar  
diol* 8 335 1977
- Frank, III The image surface of a homogeneous torso  
*AM HEART J* 47 757 1954
- Frank, III Determination of the electrical center of  
ventricular depolarization in the human heart *AM  
HEART J* 49 670 1955
- Riekkinen H and Rautaharju P M Body position  
electrode level, and respiration effects on the Frank lead  
electrocardiogram *Circulation* 53 40 1976
- Shapiro W., Berson A S and Pipberger H V Differ  
ences between supine and sitting Frank lead electrocar  
diograms, *J Electrocardiol* 9 303 1976
- Fischmann E., Cosma J., and Pipberger H V Best to  
beat and observer variation of the electrocardiogram  
*AM HEART J* 75 465 1968
- Willems J L., Poblete P F., and Pipberger H V Day  
to-day variation of the normal orthogonal electrocar  
diogram and vectorcardiogram *Circulation* 45 1057  
1972
- Kam, P M Guefira P and Pipberger H V Day to-day  
variation of the Frank electrocardiogram and vectorcar  
diogram in heart disease *AM HEART J* 88 698 1974

the superiority of fifth or fourth intercostal levels for Frank lead recordings. Nevertheless, there are persuasive reasons for electrocardiographers to agree on one choice or another. Since 12 lead electrocardiograms continue to be most widely used, we should expect to find both kinds of recordings in demand for many years to come. Perhaps the one important advantage for fifth over fourth intercostal levels is that shared electrodes in a combination conventional/Frank lead patient cable are closer to the proper locations for conventional lead recordings.

## Conclusions

The findings in this study lead to these conclusions:

1. When considering a large inhomogeneous group of subjects, differences in mean values of many commonly used amplitudes and orientations are not statistically significant among the four lead systems studied.

2. Measurement changes for individual electrocardiograms occur frequently when  $V_4$  is substituted for C, with  $R_s$  decreasing and  $R_r$  increasing in approximately 40 per cent of the records. QRS<sub>m</sub> was less often affected, most likely because of the opposite changes occurring in R and  $R_s$ .

3. When all electrodes are shifted upwards from the fifth to the fourth intercostal space for supine subjects, about 70 per cent of the records were affected. For any individual, it is not possible to predict which electrode level will result in higher electrocardiographic amplitudes.

4. Electrocardiographic measurement changes caused by electrode level changes or substitution of  $V_4$  for C are of the same order of magnitude as day to day variations.

5. Analysis programs depending on individual amplitude measurements such as decision tree programs are likely to be considerably affected by electrode placement, whether it be C alone or a complete level shift.

6. Development of criteria for analysis programs should ideally be applied only to lead systems in which electrodes are located in the same manner.

## Summary

Frank lead electrocardiograms were recorded from 149 normal and abnormal adult males using four different electrode placements. All chest electrodes were placed at (1) the fourth inter-

costal space level, (2) the fifth intercostal space level, (3) the fourth intercostal space level with  $V_4$  substituted for C, and (4) the fifth intercostal space level with  $V_4$  substituted for C.

Differences in mean values of many commonly used amplitudes and orientations were not statistically significant among the four recording methods, but amplitude differences for individual subjects were often large and difficult to predict. When  $V_4$  is substituted for C, as commonly done in some laboratories,  $R_s$  decreased and  $R_r$  increased by more than 10 per cent in about 40 per cent of the cases. In about 70 per cent of the cases,  $R_s$  and  $R_r$  changed significantly when electrode level was shifted from the fifth to the fourth intercostal space. For these 70 per cent it does not appear possible to accurately predict increase or decrease of  $R_s$ ,  $R_r$  or QRS<sub>m</sub>.

Analysis programs which depend on individual amplitude measurements are likely to be significantly affected by electrode placement. It is suggested that criteria for analysis programs developed using a specified version of the Frank system should ideally be applied only to electrocardiograms recorded in the same manner.

## REFERENCES

1. Frank R. An accurate clinically practical system for spatial vectorcardiography. *Circulation* 13:737, 1956.
2. Langner P H Jr, Okada R H, Moore S H, and Fies H L. Comparison of four orthogonal systems of vectorcardiography. *Circulation* 17:46, 1958.
3. Schmitt O H and Simonson E. The present status of vectorcardiography. *Arch Intern Med* 96:574, 1955.
4. Pipberger H V. Computer analysis of the electrocardiogram. In *Computers and biomedical research*, Vol. I, edited by R W Stacy and B H Waxman. New York: 1965, p 377. Academic Press.
5. Dunn R A, Pipberger H V, and Cornfield J. The U.S. Veterans Administration ECG analysis system. In *Computer application on ECG and VCG analysis*, edited by C Zywertz and B Schneider. Amsterdam: Oxford and New York, 1973, p 142. North Holland/American Elsevier.
6. Batschelet E. Statistical methods for the analysis of problems in animal orientation and certain biological rhythms. American Institute of Biological Sciences, Washington D C, 1965.
7. Pipberger H V et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Report of the Committee on Electrocardiography. American Heart Association. *Circulation* August 1970. News from the American Heart Association, pp 11-31.
8. Draper H W, Pfeffer C J, Stallmann F W, Littmann D, and Pipberger H V. The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system). *Circulation* 30:833, 1964.
9. Simonson E, Horie H, Okamoto N, and Schmitt O H. Effect of electrode displacement on orthogonal leads.

Table I Atrial flutter data for patients injected with lidocaine over 20 seconds

| Pt              | Drug<br>name | Weight<br>(kg) | LIDO<br>dose<br>(mg) | Serum<br>K<br>(mEq<br>/L) | Serum<br>digoxin<br>(ng/mL) | Other cardiac drugs |              |                         | Mean<br>control<br>AR<br>(beats/<br>min) | Lowest<br>AR<br>after<br>LIDO<br>(beats/<br>min) | AR<br>change<br>after<br>LIDO<br>(beats/<br>min) | Mean<br>control<br>VR<br>(beats/<br>min) | 1-6 min<br>after<br>LIDO<br>(beats/<br>min) | Mean<br>VR<br>change<br>after<br>LIDO<br>(beats/<br>min) |
|-----------------|--------------|----------------|----------------------|---------------------------|-----------------------------|---------------------|--------------|-------------------------|--|--|--|--|---|--|
|                 |              |                |                      |                           |                             | Drug                | Dose<br>(mg) | Hours<br>before<br>LIDO |  |  |  |  |   |  |
| 1               | CHD          | 104            | 100                  | 4.6                       | none                        | Prop                | 20           | 5                       | 294                                      | 268  | -26  | 147                                      | 136   | -11  |
| 2               | CHD          | 83             | 100                  | 5.6                       | undet                       |                     | none         |                         | 289                                      | 253  | -36  | 138                                      | 132   | -6   |
| 3               | CHD          | 95             | 100                  | 4.4                       | undet                       | QS                  | 400          | 5                       | 264                                      | 242  | -22  | 132                                      | 123   | -9   |
| 4               | CMP          | 0              | 100                  | 5.8                       | none                        |                     | none         |                         | 250                                      | 214  | -36  | 62                                       | 55  | -7   |
| 5               | IDIO         | 47             | 75                   | 4.4                       | none                        |                     | none         |                         | 298                                      | 270  | -28  | 80                                       | 72  | -8   |
| 6               | CHD          | 106            | 100                  | 4.9                       | < 0.5                       | QG                  | 324          | 4                       | 280                                      | 266  | -14  | 110                                      | 131   | +21  |
|                 | COPD         |                |                      |                           |                             |                     |              |                         |  |  |  |  |   |  |
| 7               | CHD          | 84             | 100                  | 4.0                       | 1.73                        | QG                  | 374          | 7                       | 308                                      | 294  | -14  | 154                                      | 146   | -8   |
| 8               | COPD         | 67             | 100                  | 5.1                       | none                        |                     | none         |                         | 318                                      | 284  | -34  | 158                                      | 147   | -11  |
| 9               | CHD          | 67             | 100                  | 4.1                       | none                        |                     | none         |                         | 268                                      | 242  | -26  | 93                                       | 120   | +27  |
| 10              | CHD          | 67             | 50                   | 6.5                       | 0.5                         |                     | none         |                         | 332                                      | 310  | -22  | 88                                       | 111   | +23  |
| 11              | IDIO         | 70             | 100                  | 4.2                       | none                        |                     | none         |                         | 264                                      | 244  | -20  | 128                                      | 124   | -4   |
| 12a             | CMP          | 84             | 100                  | 4.4                       | 0.73                        |                     | none         |                         | 298                                      | 276  | -22  | 148                                      | 138   | -10  |
| 12b             | CMP          | 78             | 100                  | 4.8                       | 1.87                        | QS                  | 400          | 0.5                     | 325                                      | 294  | -31  | 101                                      | 148   | +47  |
| 13              | CMP          | 66             | 100                  | 6.3                       | undet                       |                     | none         |                         | 288                                      | 267  | -21  | 144                                      | 133   | -11  |
| 14              | MS           | 87             | 75                   | 4.4                       | 0.71                        |                     | none         |                         | 378                                      | A Fib developed                                  |  | 91                                       | 92  | +1   |
| 15              | AS           | 75             | 100                  | 3.3                       | 0.79                        | QS                  | 500          | 1.5                     | 248                                      | 218  | -30  | 94                                       | 91  | -3   |
| 16              | COPD         | 89             | 100                  | 4.8                       | none                        |                     | none         |                         | 316                                      | 298  | -18  | 158                                      | 134   | -24  |
|                 | CHD          |                |                      |                           |                             |                     |              |                         |  |  |  |  |   |  |
| Mean $\pm$ 1 SD |              |                |                      |                           |                             |                     |              |                         | 288<br>$\pm$ 26                          | 267<br>$\pm$ 28                                  | -26<br>$\pm$ 7                                   | 119<br>$\pm$ 31                          | 120<br>$\pm$ 29                             | +0.5<br>$\pm$ 16   |

\*  $P < 0.001$ 

Abbreviations: LIDO = lidocaine; AR = atrial rate; VR = ventricular rate; CHD = coronary heart disease; CMP = congestive cardiomyopathy; IDIO = idiopathic; COPD = chronic obstructive pulmonary disease; MS = mitral stenosis; AS = aortic stenosis; undet = undetermined; prop = propranolol; QS = quinidine sulfate; QG = quinidine gluconate; A Fib = atrial fibrillation.

with atrial flutter (patient No. 12) received lidocaine injected over 20 seconds on two separate hospital admissions.

Individual lidocaine doses are listed in Tables I to III. Forty-eight of the 53 patients received a 100 mg dose of lidocaine. One patient with atrial flutter (patient No. 10) had received a lidocaine infusion which was stopped 90 minutes before the study. He was given a 50 mg dose of lidocaine. No other patient had received any lidocaine in the 24 hours prior to the study.

Continuous electrocardiographic recording in a single lead (usually MCL1) was performed for 5 minutes prior to and at least 10 minutes following lidocaine injection utilizing a Birtcher Model 335 electrocardiograph at 25 mm/sec paper speed. Blood pressure was recorded with a mercury sphygmomanometer. In patients in whom lidocaine blood levels were determined, samples were drawn through a 16 gauge Jelco needle which was

placed in the antecubital vein of the arm opposite that used for lidocaine injection. \* Serum potassium levels and serum digoxin levels were determined from venous samples drawn immediately prior to the procedure. Thirty-seven patients were given lidocaine for therapeutic indications primarily for prophylactic use immediately prior to electrocardioversion. Sixteen patients were given lidocaine for research reasons after informed consent was obtained. There were no adverse effects in any patient given lidocaine for research purposes.

Cardiac rates were determined by counting complexes on the continuous electrocardiographic write out. A mean control rate for each patient was determined by counting the entire 1 minute period immediately before lidocaine injection.

Lidocaine levels were determined by Astra Pharmaceutical Products, Inc.



# Lidocaine-induced cardiac rate changes in atrial fibrillation and atrial flutter\*

Daniel T. Danahy, MD \*\*  
Wilbert S. Aronow, MD \*\*\*  
Long Beach and Irvine Calif

In the past 15 years lidocaine has become a very important drug for treating ventricular arrhythmias.<sup>1-4</sup> Lidocaine is generally ineffective in treating supraventricular arrhythmias.<sup>5</sup> This poor response of supraventricular arrhythmias may be explained by a much less prominent effect of lidocaine on action potentials and automaticity in atrial tissue as compared to His-Purkinje fibers.<sup>6</sup> Although lidocaine is rarely used to treat atrial arrhythmias, situations commonly arise in which lidocaine is given for other indications in patients who have atrial arrhythmias as a coexisting disorder. Most often, this involves treatment of beats presumed to be premature ventricular beats (PVBs) in patients with atrial flutter or atrial fibrillation. The more widespread use of lidocaine as a routine prophylactic measure in patients with acute myocardial infarction<sup>7-9</sup> also entails administration of lidocaine to some patients with atrial flutter or atrial fibrillation.

Isolated case reports have suggested that lidocaine may be a hazardous drug in patients with atrial flutter or atrial fibrillation with a rapid

ventricular rate because of its potential to further increase ventricular rate.<sup>10</sup> The significance of these reports remains uncertain even to experts in this field<sup>11</sup> and no warning has been issued with prescription information. This problem has not been studied as regards incidence, mechanism, predictability, or predisposing factors. In the absence of adequate data, policies regarding the use of lidocaine in the presence of atrial flutter or atrial fibrillation with rapid ventricular rates vary from tight restriction to unfettered use.

In order to focus on the practical unanswered clinical questions we elected to study lidocaine as it is commonly used. Thus we administered a standard 100 mg dose which was injected rapidly. No attempt was made to eliminate other concomitantly used cardiac medications since an interaction of lidocaine with other drugs needed to be considered.

## Materials and methods

Eighteen patients with atrial flutter and 30 patients with atrial fibrillation were studied. The mean age of all patients was 62 years with a range from 42 to 85 years. In all patients 2 per cent lidocaine hydrochloride\* was injected into a vein in the antecubital or forearm area through a short segment of connecting tubing. In 16 of the patients with atrial flutter and in all 35 patients with atrial fibrillation the lidocaine was injected over 20 seconds. Three patients with atrial flutter received lidocaine injected over a 4 minute period or longer. One of these three patients (patient No. 4) had received the same dose of lidocaine injected over 20 seconds 2 days previously. One patient

\*Lidocaine Astra Pharmaceutical Worcester, Mass.

From the Cardiology Section, Long Beach Veterans Administration Hospital and the University of California College of Medicine, Irvine, Calif.

Received for publication Nov. 9, 1976.

Accepted for publication Dec. 1, 1976.

Reprint requests: Daniel T. Danahy, MD, Cardiology Section, Veterans Administration Hospital, Long Beach, Calif. 90822.

Presented at the American College of Chest Physicians Forty-second Annual Scientific Assembly, October, 1976.

Chief, Electrophysiology and Chief, Exercise Laboratory, Long Beach Veterans Administration Hospital; Assistant Professor of Medicine, University of California, Irvine.

Chief, Cardiovascular Section and Assistant Chief of Medicine for Research, Long Beach Veterans Administration Hospital; Professor of Medicine, Professor of Medical Pharmacology and Therapeutics, Professor of Community and Environmental Medicine, Vice Chief, Cardiovascular Division and Chief, Cardiovascular Research, University of California, Irvine.

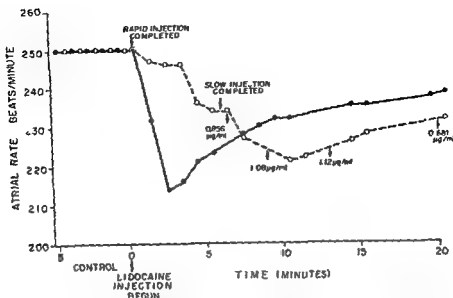


Fig 2 Atrial rate before and after lidocaine in atrial flutter patient No 4. This patient initially received 100 mg. of lidocaine injected over 20 seconds (solid line). Two days later he received 100 mg. of lidocaine injected over 5 minutes (broken line). Blood lidocaine levels were measured following the slow injection and are indicated along the curve at the time they were drawn.

Table II Atrial flutter data for patients injected with lidocaine over 4 minutes or longer

| Pt     | Diag-<br>nosis | Weight<br>(kg) | LIDO<br>dose<br>(mg) | Serum<br>K<br>mEq/L | Serum<br>digoxin<br>(ng/ml) | Other<br>cardiac<br>drugs<br>within<br>8 hours | Mean<br>control<br>AR<br>(beats/<br>min) | Lowest<br>AR after<br>LIDO<br>(beats/<br>min) | AR<br>change<br>after<br>LIDO<br>(beats/<br>min) | Mean<br>control<br>VR<br>(beats/<br>min) | Mean<br>VR<br>16 min<br>after<br>LIDO<br>(beats/<br>min) | Mean<br>VR<br>change<br>after<br>LIDO<br>(beats/<br>min) |
|--------|----------------|----------------|----------------------|---------------------|-----------------------------|--|--|---|--|--|--|--|
| 4†     | CMP            | 90             | 100                  | 5.3                 | none                        | none   | 50                                       | 29  | -29  | 62                                       | 58   | -4   |
| 17‡    | CMP            | 57             | 100                  | 4.3                 | 0.5                         | none   | 398                                      | 303   | -20  | 118                                      | 76   | 0  |
| 18‡    | IDIO           | 93             | 100                  | 4.2                 | 0.88                        | none   | 244                                      | 28  | -16  | 126                                      | 117  | -9   |
| Mean   |                |                |                      |                     |                             |  | 74                                       | 51  | -23  | 89                                       | 84   | -4   |
| ± 1 SD |                |                |                      |                     |                             |  | ± 47                                     | ± 46  | ± 7  | ± 33                                     | ± 30   | ± 5  |

P = < 0.001

† = Lidocaine injected over 6 minutes

‡ = Lidocaine injected over 4 minutes

Abbreviations: LIDO = lidocaine; AR = atrial rate; VR = ventricular rate; IDIO = idiopathic

lidocaine ( $P < 0.001$ ). In 15 of 16 atrial fibrillation patients (94 per cent) with statistically significant ventricular rate changes, the change in ventricular rate occurred abruptly within 1 minute of lidocaine injection.

In two patients with atrial fibrillation, lidocaine induced ventricular rate increases were associated with potentially serious clinical events. Fig 3 shows ECG rhythm strips before and after lidocaine in patient No 4. The lidocaine was given

prior to an electrocardioversion. One minute after the lidocaine was given, the ventricular rate accelerated by 30 beats/minute. By 4 minutes after lidocaine, the ventricular rate had increased by 40 to 50 beats/minute from the control rate and frequent long runs of wide QRS beats with a left bundle branch block configuration were seen. The cycle lengths initiating and terminating all of these salvos of wide beats were consistent with aberration in the left bundle branch. The ventric

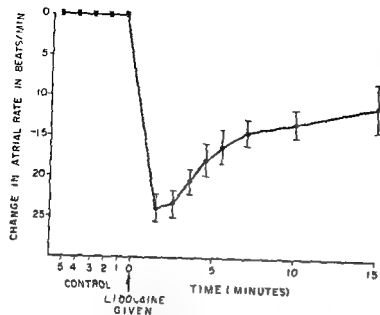


Fig 1 Mean change in atrial rate  $\pm$  SEM in the 16 patients with atrial flutter receiving rapid injection of lidocaine

A mean rate for each patient after lidocaine injection was determined by counting the entire 5 minute period from 1 to 6 minutes after lidocaine injection. Ventricular rates were counted in patients with atrial fibrillation while both atrial and ventricular rates were counted in patients with atrial flutter.

The statistical significance of any rate change in each individual patient was determined by using Student's *t* test. The 5 minute time period immediately before and the 1 to 6 minute time period after lidocaine injection were each divided into ten 30 second segments for this analysis. The statistical significance of changes for the entire group of patients with atrial flutter and the group with atrial fibrillation were determined using Student's *t* test for correlated means. Correlation coefficients were calculated using Pearson's product moment. For calculations of correlation coefficients, serum digoxin levels reported by the laboratory as  $< 0.5$  ng/ml were considered to be 0.25 ng/ml. Patients who were receiving digoxin but in whom serum levels were not determined (marked undet in Tables I to III) were excluded from these calculations.

## Results

Table I shows the clinical data and response to lidocaine in the 16 patients with atrial flutter given lidocaine over 20 seconds. Patient No 14 developed transient atrial fibrillation following lidocaine injection. The other 15 patients all

showed a prompt decrease in atrial rate after lidocaine. The peak decrease in atrial rate occurred 1 to 2 minutes after lidocaine injection with a gradual return towards the control atrial rate over the next 10 to 20 minutes of recording (Fig 1).

Table II indicates patients No 17 and 18 were given lidocaine over 4 minutes rather than over 20 seconds. Patient No 4 received 100 mg of lidocaine injected over 20 seconds one day and 100 mg of lidocaine injected over 6 minutes 2 days later (Table II and Fig 2). These three patients showed slowing of the atrial rate similar to that observed in patients with lidocaine injected over 20 seconds.

This consistent decrease in atrial rate after lidocaine was accompanied by a variable and unpredictable change in ventricular rate. The ventricular rate for the entire group of patients with atrial flutter and rapid lidocaine injection was unchanged after the lidocaine injection. However, three individual patients (patients No 6, 9, and 12) significantly increased their ventricular rate ( $P < 0.001$ ) after lidocaine. The mean rate increases in these three patients during the period from 1 to 6 minutes after lidocaine were 21, 27, and 47 beats/minute respectively.

In seven patients the ventricular rate decreased significantly ( $P < 0.001$ ) after lidocaine. The patients with a fall in ventricular rate generally had no change in A-V conduction. Thus slowing of the atrial rate was accompanied by slowing of the ventricular rate. In patients No 6, 9, and 12 as the atrial rate slowed the A-V conduction ratio decreased and the ventricular rate increased. The atrial flutter rate changes and significant ventricular rate changes occurred abruptly with 1 minute of lidocaine injection.

Table III shows the clinical data and response to lidocaine of the patients with atrial fibrillation. Considering the group as a whole, the ventricular rate increased 6 beats/minute following lidocaine ( $P < 0.01$ ). The ventricular rate increase in some individual patients was much greater and was clinically relevant. In 14 individual patients the ventricular rate increased significantly after lidocaine as compared to the control period immediately prior to lidocaine injection ( $P < 0.001$ ). In three of these patients the rate increase was greater than 20 beats/minute. In two patients the ventricular rate significantly decreased after

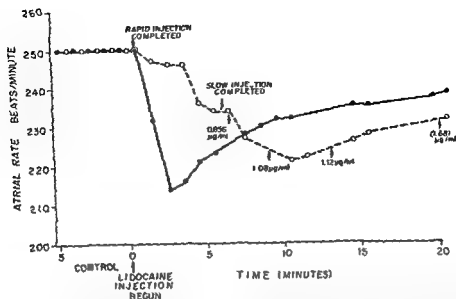


Fig 2 Atrial rate before and after lidocaine in atrial flutter patient No 4. This patient initially received 100 mg of lidocaine injected over 20 seconds (solid line). Two days later he received 100 mg of lidocaine injected over 6 minutes (broken line). Blood lidocaine levels were measured following the slow injection and are indicated along the curve at the time they were drawn.

Table II Atrial flutter data for patients injected with lidocaine over 4 minutes or longer

| Pt     | Diagnosis | Weight (kg) | LIDO dose (mg) | Serum K mEq/L | Serum digoxin (ng/ml) | Other cardiac drugs within 8 hours | Mean control AR (beats/min) | Lowest AR after LIDO (beats/min) | AR change after LIDO (beats/min) | Mean control VR (beats/min) | Mean VR 1-6 min after LIDO (beats/min) | Mean VR change after LIDO (beats/min) |
|--------|-----------|-------------|----------------|---------------|-----------------------|------------------------------------|-----------------------------|----------------------------------|----------------------------------|-----------------------------|--|---------------------------------------|
| 4†     | CMP       | 70          | 100            | 5.3           | none                  | none                               | 250                         | 221                              | -29                              | 62                          | 58                                     | -4                                    |
| 12†    | CMP       | 57          | 100            | 4.3           | 0.5                   | none                               | 3.8                         | 30.3                             | -25                              | 78                          | 78                                     | 0                                     |
| 18‡    | IDIO      | 83          | 100            | 4.2           | 0.88                  | none                               | 244                         | 228                              | -16                              | 126                         | 117                                    | -9                                    |
| Mean   |           |             |                |               |                       |                                    | 274                         | 251                              | -23                              | 89                          | 84                                     | -4                                    |
| ± 1 SD |           |             |                |               |                       |                                    | ± 47                        | ± 46                             | ± 7                              | ± 33                        | ± 30                                   | ± 5                                   |

P = < 0.001

† = Lidocaine injected over 20 minutes

‡ = Lidocaine injected over 4 minutes

Abbreviations: LIDO = lidocaine; AR = atrial rate; VR = ventricular rate; IDIO = idopathic

lidocaine ( $P < 0.001$ ). In 15 of 16 atrial fibrillation patients (94 per cent) with statistically significant ventricular rate changes the change in ventricular rate occurred abruptly within 1 minute of lidocaine injection.

In two patients with atrial fibrillation lidocaine induced ventricular rate increases were associated with potentially serious clinical events. Fig 3 shows ECG rhythm strips before and after lidocaine in patient No 4. The lidocaine was given

prior to an electrocardioversion. One minute after the lidocaine was given the ventricular rate accelerated by 30 beats/minute. By 4 minutes after lidocaine the ventricular rate had increased by 40 to 50 beats/minute from the control rate and frequent long runs of wide QRS beats with a left bundle branch block configuration were seen. The cycle lengths initiating and terminating all of these salvos of wide beats were consistent with aberration in the left bundle branch. The ventric

Table III Atrial fibrillation data

| Pt             | Diagnosis       | Weight<br>(kg) | LIDO<br>dose<br>(mg) | Serum<br>K<br>(mEq /L) | Serum<br>digoxin<br>(ng /ml) | Other cardiac drugs |              |                         | Mean<br>control VR<br>(beats/min) | Mean VR<br>16 min<br>after LIDO<br>(beats/min) | Mean VR<br>change<br>after LIDO<br>(beats/min) |
|----------------|-----------------|----------------|----------------------|------------------------|------------------------------|---------------------|--------------|-------------------------|-----------------------------------|--|--|
|                |                 |                |                      |                        |                              | Drug                | Dose<br>(mg) | Hours<br>before<br>LIDO |                                   |  |  |
| 1              | CHD             | 73             | 110                  | 4.2                    | none                         | QS                  | 400          | 4                       | 113                               | 100  | -13  |
| 2              | CHD CHF         | 71             | 100                  |                        | undet                        | QS                  | 200          | 6                       | 98                                | 92   | -6   |
| 3              | IDIO            | 86             | 100                  | 4.5                    | none                         |                     | none         |                         | 81                                | 81   | +10  |
| 4              | CHD             | 92             | 100                  | 4.4                    | 0.71                         | QS                  | 200          | 2.5                     | 142                               | 176  | +34  |
| 5              | AI              | 85             | 100                  | 4.5                    | none                         |                     | none         |                         | 53                                | 58   | +5   |
| 6              | AS COPD         | 58             | 100                  | 4.4                    | 3.7                          |                     | none         |                         | 113                               | 115  | +2   |
| 7              | IDIO            | 134            | 125                  | 5.0                    | 0.85                         |                     | none         |                         | 109                               | 120  | +11†   |
| 8              | CHD             | 125            | 125                  | 4.3                    | <0.5                         | QG                  | 324          | 4                       | 101                               | 116  | +15  |
| 9              | IDIO            | 100            | 100                  | 4.3                    | <0.5                         | QG                  | 324          | 3.5                     | 86                                | 93   | +7   |
| 10             | CHD             | 55             | 100                  | 5.4                    | 0.80                         |                     | none         |                         | 93                                | 101  | +8   |
| 11             | CHD CHF         | 90             | 100                  | 4.8                    | 1.7                          | QG                  | 324          | 5                       | 111                               | 103  | +8   |
| 12             | MS              | 74             | 100                  | 3.8                    | undet                        | QG                  | 324          | 4                       | 97                                | 110  | +13  |
| 13             | COPD CHD        | 64             | 100                  | 5.1                    | undet                        |                     | none         |                         | 171                               | 181  | +10†   |
| 14             | HT              | 53             | 100                  | 3.6                    | none                         |                     | none         |                         | 111                               | 90   | +21  |
| 15             | MS              | 72             | 100                  | 3.8                    | <0.5                         | QG                  | 324          | 5                       | 142                               | 142  | 0  |
| 16             | HT              | 72             | 100                  |                        | undet                        | PROP                | 20           | 6                       | 140                               | 136  | +4   |
| 17             | CHD             | 62             | 100                  | 4.6                    | 1.45                         |                     | none         |                         | 118                               | 105  | +13  |
| 18             | IDIO PC         | 82             | 100                  | 3.4                    | <0.5                         |                     | none         |                         | 140                               | 140  | 0  |
| 19             | IHSS            | 100            | 100                  | 4.0                    | none                         | QS                  | 300          | 1                       | 91                                | 106  | +15  |
| 20             | COPD MS         | 59             | 100                  | 3.7                    | 1.95                         |                     | none         |                         | 85                                | 89   | +4   |
| 21             | MS              | 66             | 100                  | 4.1                    | 74                           |                     | none         |                         | 65                                | 71   | +6   |
| 22             | CHD AS          | 67             | 100                  | 4.4                    | 1.51                         | QS                  | 300          | 4.5                     | 86                                | 90   | +4   |
| 23             | CHD             | 87             | 100                  | 4.5                    | 2.25                         | QG                  | 324          | 4                       | 123                               | 129  | +6   |
| 24             | CMP             | 75             | 100                  | 3.8                    | 1.85                         |                     | none         |                         | 72                                | 73   | +1   |
| 25             | CHD COPD        | 84             | 100                  | 4.7                    | 1.15                         |                     | none         |                         | 106                               | 103  | +3   |
| 26             | COPD            | 88             | 100                  | 4.1                    | 2.13                         |                     | none         |                         | 136                               | 136  | 0  |
| 27             | CHD             | 82             | 100                  | 3.6                    | 1.15                         |                     | none         |                         | 69                                | 64   | +5   |
| 28             | CMP             | 77             | 100                  | 4.6                    | 1.00                         |                     | none         |                         | 119                               | 128  | +9   |
| 29             | CHD CHF<br>COPD | 68             | 100                  | 3.5                    | undet                        |                     | none         |                         | 122                               | 117  | +5   |
| 30             | CHD COPD        | 67             | 100                  | 2.7                    | 2.6                          |                     | none         |                         | 74                                | 75   | +1   |
| 31             | IDIO            | 93             | 100                  | 5.0                    | undet                        | QG                  | 324          | 6                       | 92                                | 102  | +10  |
| 32             | MS CHD          | 70             | 100                  | 5.0                    | 1.00                         | QS                  | 400          | 1                       | 78                                | 83   | +5   |
| 33             | CMP             | 56             | 100                  | 4.5                    | <0.5                         | QS                  | 300          | 3.5                     | 108                               | 133  | +25  |
| 34             | CMP             | 88             | 100                  | 3.7                    | <0.5                         | QS                  | 300          | 4                       | 74                                | 98   | +24  |
| 35             | CHD COPD        | 71             | 100                  | 4.2                    | 0.88                         |                     | none         |                         | 111                               | 102  | +9   |
| Mean<br>± 1 SD |                 |                |                      |                        |                              |                     |              |                         | 102<br>± 26                       | 108<br>± 28                                    | +6<br>± 10                                     |

\* P &lt; 0.001

† P &lt; 0.005

Abbreviations: LIDO = lidocaine; VR = ventricular rate; COPD = chronic obstructive pulmonary disease; MS = mitral stenosis; CHD = coronary heart disease; AS = aortic stenosis; CMP = congestive cardiomyopathy; IDIO = idiopathic; CHF = congestive heart failure; AI = aortic insufficiency; HT = hypertension; PC = pericarditis; IHSS = idiopathic hypertrophic subaortic stenosis; undet = undetermined; QS = quinidine sulfate; QG = quinidine gluconate; PROP = propranolol.

ular rate increase and long runs of aberrant beats (many lasting 30 seconds or more) persisted for 17 minutes at which time the elective cardioversion was successfully performed without difficulty. The patient had no symptoms and no change in blood pressure during this period of ventricular rate increase. A serum lidocaine level drawn 8 minutes after the lidocaine injection, in the

midportion of the period of ventricular acceleration, was 1.47 µg/ml (lidocaine base).

Patient No. 13 in Table III was hospitalized because of marked dyspnea with a history of severe chronic obstructive lung disease. He was found to be in atrial fibrillation with a ventricular rate of 170 beats/minute. The patient had been taking digoxin 0.5 mg daily. His serum digoxin

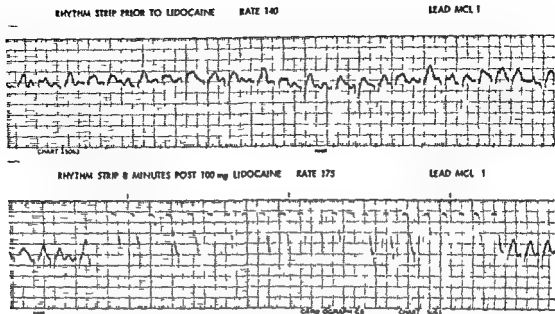


Fig 3 Electrocardiographic rhythm strips before and after lidocaine injection in atrial fibrillation patient No. 4

and K levels were unknown at that time. It was elected to cardiovert the patient and 100 mg of lidocaine were given over 20 seconds as a prophylactic measure prior to the cardioversion. One minute after the lidocaine was given the ventricular rate increased to between 180 and 190 beats/minute. The blood pressure, which had been 110/70, was then unobtainable and the patient appeared confused and diaphoretic. The patient was cardioverted to normal sinus rhythm and recovered. The adverse effect seems clearly related to lidocaine but it is uncertain whether the primary effect was ventricular rate acceleration or hemodynamic depression followed by a secondary ventricular rate increase. This was the only patient in whom a fall in blood pressure occurred after lidocaine injection.

Serial lidocaine blood levels were determined in a small representative sample of patients to document the range of blood levels obtained with this method of administration. Fig 4 demonstrates therapeutic blood levels during the time of lidocaine-induced atrial and ventricular rate changes. The curve for lidocaine blood levels closely mirrors the curve for atrial rate decrease after lidocaine (Fig 1).

Baseline atrial and ventricular rates, serum potassium levels, serum digoxin levels, and lidocaine dose/kg of body weight were not useful in predicting either atrial or ventricular rate

changes after lidocaine. The only significant correlation was between the serum digoxin level and the degree of ventricular rate change after lidocaine in atrial fibrillation patients ( $r = -0.38$ ,  $P < 0.05$ ).

Quinidine did have an important influence on ventricular rate changes. Nine of 15 atrial fibrillation patients (60 per cent) who were also receiving quinidine significantly increased their ventricular rate after lidocaine, while only five of 20 atrial fibrillation patients (25 per cent) who were not receiving quinidine significantly increased their ventricular rate ( $P < 0.01$ ). Two of three atrial flutter patients and three of three atrial fibrillation patients whose ventricular rate increased by more than 20 beats/minute were receiving quinidine.

### Discussion

These data help clarify the response to lidocaine in patients with atrial flutter and atrial fibrillation. Atrial flutter rates show an immediate and consistent fall when lidocaine is administered. This might be explained by lidocaine's ability to decrease conduction velocity in atrial tissue. The atrial slowing occurred whether the lidocaine was injected slowly over several minutes or was injected rapidly over 20 seconds (a method of administration which results in transiently toxic arterial lidocaine levels).<sup>11</sup> Fig 2 demon-

Table III Atrial fibrillation data

| Pt     | Diagnosis | Weight<br>(kg) | LIDO<br>dose<br>(mg) | Serum<br>K<br>(mEq/L) | Serum<br>digoxin<br>(ng/ml) | Other cardiac drugs |              |                         | Mean VR<br>control VR<br>(beats/min) | Mean VR<br>16 min<br>after LIDO<br>(beats/min) | Mean VR<br>change<br>after LIDO<br>(beats/min) |
|--------|-----------|----------------|----------------------|-----------------------|-----------------------------|---------------------|--------------|-------------------------|--------------------------------------|--|--|
|        |           |                |                      |                       |                             | Drug                | Dose<br>(mg) | Hours<br>before<br>LIDO |                                      |  |  |
| 1      | CHD       | 73             | 110                  | 4.2                   | none                        | QS                  | 400          | 4                       | 113                                  | 100  | -13  |
| 2      | CHD CHF   | 71             | 100                  |                       | undet                       | QS                  | 200          | 6                       | 98                                   | 92   | -6   |
| 3      | IDIO      | 86             | 100                  | 4.5                   | none                        |                     | none         |                         | 81                                   | 91   | +10  |
| 4      | CHD       | 92             | 100                  | 4.4                   | 0.71                        | QS                  | 200          | 2.5                     | 142                                  | 176  | +34  |
| 5      | AI        | 85             | 100                  | 4.5                   | none                        |                     | none         |                         | 53                                   | 58   | +5   |
| 6      | AS COPD   | 58             | 100                  | 4.4                   | 3.7                         |                     | none         |                         | 113                                  | 115  | +2   |
| 7      | IDIO      | 134            | 125                  | 5.0                   | 0.85                        |                     | none         |                         | 109                                  | 120  | +11†   |
| 8      | CHD       | 125            | 125                  | 4.3                   | <0.5                        | QG                  | 324          | 4                       | 101                                  | 116  | +15  |
| 9      | IDIO      | 100            | 100                  | 4.3                   | <0.5                        | QG                  | 324          | 3.5                     | 86                                   | 93   | +7   |
| 10     | CHD       | 68             | 100                  | 5.4                   | 0.80                        |                     | none         |                         | 93                                   | 101  | +8   |
| 11     | CHD CHF   | 90             | 100                  | 4.8                   | 1.7                         | QG                  | 324          | 5                       | 98                                   | 103  | +5   |
| 12     | MS        | 74             | 100                  | 3.8                   | undet                       | QG                  | 324          | 4                       | 95                                   | 110  | +15  |
| 13     | COPD CHD  | 64             | 100                  | 5.1                   | undet                       |                     | none         |                         | 171                                  | 181  | +10†   |
| 14     | HT        | 53             | 100                  | 3.6                   | none                        |                     | none         |                         | 88                                   | 90   | +2   |
| 15     | MS        | 72             | 100                  | 3.8                   | <0.5                        | QG                  | 324          | 5                       | 142                                  | 142  | 0  |
| 16     | HT        | 72             | 100                  |                       | undet                       | PROP                | 20           | 6                       | 140                                  | 136  | -4   |
| 17     | CHD       | 62             | 100                  | 4.6                   | 1.45                        |                     | none         |                         | 118                                  | 105  | -13  |
| 18     | IDIO PC   | 82             | 100                  | 3.4                   | <0.5                        |                     | none         |                         | 140                                  | 140  | 0  |
| 19     | IHSS      | 100            | 100                  | 4.0                   | none                        | QS                  | 300          | 1                       | 91                                   | 106  | +15  |
| 20     | COPD MS   | 59             | 100                  | 3.7                   | 1.95                        |                     | none         |                         | 85                                   | 89   | +4   |
| 21     | MS        | 66             | 100                  | 4.1                   | 74                          |                     | none         |                         | 65                                   | 71   | +6   |
| 22     | CHD AS    | 67             | 100                  | 4.4                   | 1.51                        | QS                  | 300          | 4.5                     | 86                                   | 95   | +9†  |
| 23     | CHD       | 85             | 100                  | 4.5                   | 2.25                        | QG                  | 324          | 4                       | 123                                  | 129  | +6   |
| 24     | CMP       | 75             | 100                  | 3.8                   | 1.85                        |                     | none         |                         | 72                                   | 73   | +1   |
| 25     | CHD COPD  | 84             | 100                  | 4.7                   | 1.15                        |                     | none         |                         | 106                                  | 103  | -3   |
| 26     | COPD      | 88             | 100                  | 4.1                   | 2.13                        |                     | none         |                         | 136                                  | 136  | 0  |
| 27     | CHD       | 82             | 100                  | 3.6                   | 1.15                        |                     | none         |                         | 69                                   | 64   | -5   |
| 28     | CMP       | 77             | 100                  | 4.6                   | 1.00                        |                     | none         |                         | 119                                  | 128  | +9   |
| 29     | CHD CHF   | 68             | 100                  | 3.5                   | undet                       |                     | none         |                         | 122                                  | 117  | -5   |
| 30     | CHD COPD  | 67             | 100                  | 2.7                   | 2.6                         |                     | none         |                         | 74                                   | 75   | +1   |
| 31     | IDIO      | 93             | 100                  | 5.0                   | undet                       | QG                  | 324          | 6                       | 92                                   | 102  | +10  |
| 32     | MS CHD    | 70             | 100                  | 5.0                   | 1.00                        | QS                  | 400          | 1                       | 78                                   | 83   | +5   |
| 33     | CMP       | 56             | 100                  | 4.5                   | <0.5                        | QS                  | 300          | 3.5                     | 108                                  | 133  | +25  |
| 34     | CMP       | 88             | 100                  | 3.7                   | <0.5                        | QS                  | 300          | 4                       | 74                                   | 98   | +24  |
| 35     | CHD COPD  | 71             | 100                  | 4.2                   | 0.88                        |                     | none         |                         | 93                                   | 102  | +9   |
| Mean   |           |                |                      |                       |                             |                     |              |                         | ± 26                                 | ± 28   | ± 10   |
| ± 1 SD |           |                |                      |                       |                             |                     |              |                         |                                      |  |  |

\* P &lt; 0.001

† P &lt; 0.005

Abbreviations LIDO = lidocaine VR = ventricular rate COPD = chronic obstructive pulmonary disease MS = mitral stenosis CHD = coronary heart disease AS = aortic stenosis CMP = congestive cardiomyopathy IDIO = idiopathic CHF = congestive heart failure AI = aortic insufficiency HT = hypertension PC = pericarditis IHSS = idiopathic hypertrophic subaortic stenosis undet = undetermined QS = quinidine sulfate QG = quinidine gluconate PROP = propranolol

ular rate increase and long runs of aberrant beats (many lasting 30 seconds or more) persisted for 17 minutes at which time the elective cardioversion was successfully performed without difficulty. The patient had no symptoms and no change in blood pressure during this period of ventricular rate increase. A serum lidocaine level drawn 8 minutes after the lidocaine injection in the

midportion of the period of ventricular acceleration was 1.47 µg/ml (lidocaine base).

Patient No. 13 in Table III was hospitalized because of marked dyspnea with a history of severe chronic obstructive lung disease. He was found to be in atrial fibrillation with a ventricular rate of 170 beats/minute. The patient had been taking digoxin 0.5 mg daily. His serum digoxin

terms of reported cases is greatest in atrial flutter. Lidocaine should be used with great caution if at all in patients with atrial flutter and 2:1 A-V response.

The second problem lidocaine may create when used in atrial fibrillation or flutter with a rapid ventricular rate is that of aberrant conduction. Wide QRS beats presumed to be PVBs are the usual reason for giving lidocaine to patients with atrial tachyarrhythmias. A clear distinction between ventricular ectopy and aberrant conduction of supraventricular impulses may be very difficult in such patients. Lidocaine may accelerate the ventricular rate and aggravate the problem of aberrant conduction (Fig 3). The depressant effect of lidocaine on ventricular conduction tissue may also contribute to aberration particularly in patients with underlying fascicular conduction disease given rapid bolus injections.

We share Marriott and Biezas abhorrence of the lidocaine reflex when faced with atrial fibrillation or flutter a rapid ventricular rate and frequent wide QRS complexes. Measures to slow the ventricular rate are often the most appropriate therapy. However, since a precise diagnosis may not be possible without His bundle recordings and since alternative methods of treatment may also be hazardous, we believe lidocaine does have a role in some of these circumstances if used with discrimination.

The data presented here demonstrate that clinically significant ventricular acceleration in patients with atrial flutter or atrial fibrillation who are given lidocaine is not a rare phenomenon. In the presence of quinidine it is a very common phenomenon. Lidocaine should be used with caution in the presence of atrial arrhythmias with an already rapid ventricular rate.

### Summary

To assess atrial and ventricular rate changes after lidocaine injection 18 atrial flutter patients and 35 atrial fibrillation patients were given intravenous lidocaine mean dose 100 mg. Continuous electrocardiographic recording for 5 minutes before and at least 10 minutes after lidocaine injection was used to determine rate changes. The atrial flutter rate decreased after lidocaine in 17 of 18 patients (94 per cent) mean maximal decrease 27 beats/minute. The ventricular rate

response in atrial flutter was variable but in three patients increased 21, 27 and 47 beats/minute respectively ( $P < 0.001$ ). In atrial fibrillation the mean ventricular rate after rapid lidocaine injection increased six beats/minute ( $P < 0.01$ ). In three of 35 atrial fibrillation patients (9 per cent) the ventricular rate increase was greater than 20 beats/minute ( $P < 0.001$ ) and in two patients (6 per cent) the ventricular rate increase was associated with potentially serious clinical events. Lidocaine induced ventricular rate increases are common in atrial flutter and fibrillation particularly in patients who are also receiving quinidine.

The authors wish to express their appreciation to M. H. Meyer MD, Astra Pharmaceutical Products Inc. for performing the lidocaine blood levels.

### REFERENCES

1. Gianelly R, Von der Groeben J O, Spivack A P et al. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *N Engl J Med* 277:1215, 1967.
2. Spracklen F H N, Kumerling J J, Besterman E M M et al. Use of lignocaine in treatment of cardiac arrhythmias. *Br Med J* 1:89, 1968.
3. Flenskjeld-Jensen E and Sandoe E. Lidocaine as an antiarrhythmic agent. *Acta Med Scand* 185:297, 1969.
4. Grossman J I, Lubow L A, Friden J, et al. Lidocaine in cardiac arrhythmias. *Arch Intern Med* 121:396, 1968.
5. Mandel W J and Bigger J T, Jr. Electrophysiologic effects of lidocaine on isolated canine and rabbit atrial tissue. *J Pharmacol Exp Ther* 178:81, 1971.
6. Lee K I, Wellens H J, Van Capelle F J et al. Lidocaine in the prevention of primary ventricular fibrillation. *N Engl J Med* 291:1374, 1974.
7. Wyman M G and Hammersmith L. Comprehensive treatment plan for the prevention of primary ventricular fibrillation in acute myocardial infarction. *Am J Cardiol* 33:661, 1974.
8. Marriott H J L and Biezas C F. Alarming ventricular acceleration after lidocaine administration. *Chest* 61:652, 1972.
9. Adamson A R and Spracklen F H N. Atrial flutter with block—contraindication to use of lignocaine. *Br Med J* 2:423, 1968.
10. Julian D G, Killip T, Marriott H J L et al. General discussion in Lidocaine in the treatment of ventricular arrhythmias. Scott D B and Julian D G, eds. Edinburgh 1971. Churchill Livingstone, p. 273.
11. Collinsworth K A, Kalman M M and Harrison D C. The clinical pharmacology of lidocaine as an antiarrhythmic drug. *Circulation* 50:1217, 1974.
12. Sun, B N and Vaughan Williams E M. Effect of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. *Circ Res* 29:286, 1971.
13. Roes, J C and Dunning A J. Effects of lidocaine on impulse formation and conduction defects in man. *Am Heart J* 89:686, 1975.



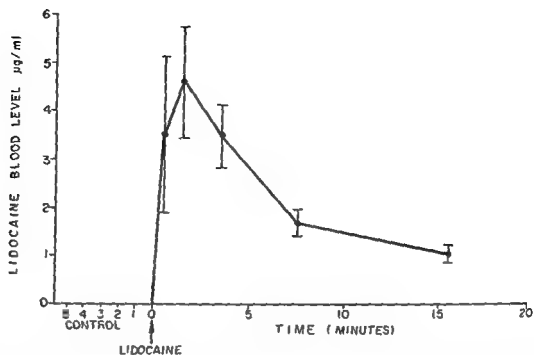


Fig 4 Mean lidocaine blood levels  $\pm 1$  SEM before and after rapid lidocaine injection in five representative patients (atrial fibrillation patients No 18 and 25 and atrial flutter patients No 5 ■ and 12a)

strates that atrial slowing was present when lidocaine blood levels were in the low therapeutic range

The two previous case reports of serious ventricular acceleration after lidocaine administration in patients with atrial flutter also demonstrated atrial slowing.<sup>11</sup> Slowing of the atrial flutter rate with lidocaine may be an important factor affecting the more clinically crucial ventricular rate response. A decrease in the number of impulses reaching the A V node may result in a greater number of impulses per minute conducted to the ventricles.

Another very important consideration regarding lidocaine induced ventricular rate changes is the effect of lidocaine on A V conduction velocity and refractory periods. Changes could result either from direct effects of lidocaine on the A V node or from alterations in the autonomic state. A V conduction and refractory periods cannot be measured by standard techniques in the presence of atrial flutter or atrial fibrillation. Previous studies reported in patients with sinus rhythm have shown no consistent effect of lidocaine on A V node refractoriness or conduction although a shortening of the effective refractory period was noted in a few patients.<sup>12,13</sup> These parameters have not been measured when quinidine is also present, a factor which seems quite relevant in light of our data. Further studies are necessary to

evaluate this interaction between lidocaine and quinidine.

It had been anticipated that serum potassium levels and serum digoxin levels would be important in influencing lidocaine's effects on cardiac rates. Lidocaine's depressant effect on cardiac conduction tissue has been shown to increase with increasing potassium concentrations<sup>14</sup> while digoxin has clinically important effects on the A V node which slow the ventricular rate in atrial flutter and in atrial fibrillation. In contrast to the clear interaction from quinidine there was no significant influence from serum potassium levels and only a weak negative correlation of serum digoxin levels with ventricular rate changes. The most dramatic ventricular acceleration (atrial flutter patient No 12b) occurred with a serum digoxin level of 1.84 ng/ml. Thus digoxin affords incomplete protection against ventricular rate increases in patients with atrial flutter or atrial fibrillation who are given lidocaine.

Ventricular rate increases after lidocaine in patients with either atrial flutter or atrial fibrillation are most likely to cause problems when the ventricular rate is already rapid. Clinical problems may develop from either of two mechanisms.

First of all the rate increase itself may be marked enough to seriously impair cardiac output. This danger both theoretically and in

# Cholelithiasis A frequent complication of artificial heart valve replacement

Earl C Harrison MD  
E John Roschke PhD\*  
Harvey I Meyers MD  
W Allan Edmiston MD  
Linda S Chan PhD  
Dorothy Tatter MD  
Francis YK Lau MD  
*Los Angeles and Pasadena Calif*

A mild usually well compensated intravascular hemolytic process has been described in patients with valvular heart disease<sup>1-3</sup> especially when the aortic valve is severely damaged<sup>4-6</sup>. Numerous studies<sup>7-9</sup> have demonstrated a greater yet still mild degree of hemolysis associated with various types of normally functioning valve prostheses. The hemolytic process can become severe and inadequately compensated when ball variance<sup>11</sup> or paraprosthetic leaks develop.

A report by Merendino and Manhas<sup>7</sup> in June 1973 implicated valve prostheses with the development of gallstones. In 1958 Glenn and Redo reported an increased prevalence of gallstones in women with mitral valve disease. With this limited evidence that mild mechanical hemolysis is not as innocuous as considered previously a study was undertaken to determine the prevalence of gallstones in prosthetic valve recipients followed in the Los Angeles County-USC Medical Center (LAC-USC-MC) outpatient clinic. For comparative purposes a survey of autopsied cases was also undertaken to determine the prevalence of gallstones in patients with

rheumatic and/or other forms of severe valvular heart disease.

## Methods

Our study group (Group A) consists of 46 valve prosthesis patients who attended our clinic at LAC-USC-MC and had survived valve replacement for 18 months or longer. Sixteen had Smeloff Cutter aortic valves, two had Bjork Shiley aortic valves, three had Starr Edwards aortic valves, eighteen had Kay Shiley mitral valves, three had Starr Edwards mitral valves, and four had two implanted prostheses of the Smeloff Cutter and/or Kay Shiley type. This group of patients represented three ethnic groups and ages that ranged from 20 to 69 years. All of the patients had normally functioning prosthetic valves and there was no evidence to indicate the presence of ball or poppet variance or paraprosthetic leaks.

An oral cholecystogram was performed in each of these patients to determine the presence or absence of gallstones. A standard dose of iopanoic acid USP (Telepaque) was utilized when required, a double dose was employed for better visualization of the gallbladder. The presence of a mild hemolytic process was established in nearly all cases utilizing one or more of the following determinations: serum haptoglobin, lactic dehydrogenase, total and direct acting bilirubin, serial reticulocyte counts, serial hematocrits, and urine examination for hemosiderin.

From the Department of Medicine and Cardiology Section, Los Angeles County-USC Medical Center, Los Angeles, Calif. (E.C.H., E.J.R., H.I.M., W.A.E., L.S.C., D.T., F.Y.K.L.).  
Presented at the 1973 American Heart Association Scientific Sessions, San Francisco, Calif.

Received for publication Feb 9 1977

Accepted for publication May 19 1977

Reprint requests: Earl C Harrison MD, Box 210, 1200 N. State, Los Angeles County-USC Medical Center, Los Angeles, CA 90033.

Jet Propulsion Laboratory, Pasadena, Calif.

- 14 Rosen K M Lau S H Weiss M H et al The effect of lidocaine on atrioventricular and intraventricular conduction in man Am J Cardiol 25 1 1971
- 15 Josephson M E Caracta A R Lau S H et al Effects of lidocaine on refractory periods in man AM HEART J 84 778, 1972
- 16 Kunkel F Rowland M and Scheinman M M The electrophysiologic effects of lidocaine in patients with intraventricular conduction defects Circulation 49 894, 1974
- 17 Bekheit S Murtagh J G Morton P et al Effect of lignocaine on conducting system of human heart, Br Heart J 35 305 1973
- 18 Gupta P K Lichstein E and Chadds K D Lidocaine induced heart block in patients with bundle branch block Am J Cardiol 33 487 1974

### Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. P.O. Box 765, Schenectady, N.Y. 12301 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

# Cholelithiasis A frequent complication of artificial heart valve replacement

Earl C Harrison MD  
E John Roschke PhD\*  
Harvey I Meyers MD  
W Allan Edmiston MD  
Linda S Chan PhD  
Dorothy Tatter MD  
Francis Y K Lau MD  
*Los Angeles and Pasadena Calif*

A mild usually well compensated intravascular hemolytic process has been described in patients with valvular heart disease, especially when the aortic valve is severely damaged. Numerous studies<sup>1-4</sup> have demonstrated a greater yet still mild degree of hemolysis associated with various types of normally functioning valve prostheses. The hemolytic process can become severe and inadequately compensated when ball variance<sup>1,2</sup> or paraprosthesis leaks develop.<sup>5-7</sup>

A report by Merendino and Manhas<sup>8</sup> in June 1973 implicated valve prostheses with the development of gallstones. In 1958 Glenn and Redo reported an increased prevalence of gallstones in women with mitral valve disease. With this limited evidence that mild mechanical hemolysis is not as innocuous as considered previously a study was undertaken to determine the prevalence of gallstones in prosthetic valve recipients followed in the Los Angeles County-USC Medical Center (LAC-USC-MC) outpatient clinic. For comparative purposes a survey of autopsied cases was also undertaken to determine the prevalence of gallstones in patients with

rheumatic and/or other forms of severe valvular heart disease.

## Methods

Our study group (Group A) consists of 46 valve prosthesis patients who attended our clinic at LAC-USC-MC and had survived valve replacement for 18 months or longer. Sixteen had Smeloff Cutter aortic valves, two had Björk Shiley aortic valves, three had Starr Edwards aortic valves, eighteen had Kay Shiley mitral valves, three had Starr Edwards mitral valves, and four had two unimplanted prostheses of the Smeloff Cutter and/or Kay Shiley type. This group of patients represented three ethnic groups and ages that ranged from 20 to 69 years. All of the patients had normally functioning prosthetic valves and there was no evidence to indicate the presence of ball or poppet variance or paraprosthesis leaks.

An oral cholecystogram was performed in each of these patients to determine the presence or absence of gallstones. A standard dose of iopanoic acid USP (Telepaque) was utilized, when required a double dose was employed for better visualization of the gallbladder. The presence of a mild hemolytic process was established in nearly all cases utilizing one or more of the following determinations: serum haptoglobin, lactic dehydrogenase, total and direct acting bilirubin, serial reticulocyte counts, serial hematocrits, and urine examination for hemosiderin.

From the Department of Medicine, Cardiology Section, Los Angeles County-USC Medical Center, Los Angeles, California; and the Jet Propulsion Laboratory, Pasadena, California.

Received for publication Feb 9, 1977.

Accepted for publication May 29, 1977.

Reprint requests: Earl C Harrison MD, Box 310, 1200 N State St, Los Angeles County-USC Medical Center, Los Angeles, CA 90033.

Jet Propulsion Laboratory, Pasadena, Calif.

**Table 1** Comparison of prevalence of gallstones in the heart valve prosthesis recipients (Group A) rheumatic heart disease cases (Group B), and severe valvular heart disease cases (Group C)

| Age<br>Intervals     | Group A       | Group B          | Group C       | Results of statistical<br>tests for difference |                  |
|----------------------|---------------|------------------|---------------|--|------------------|
|                      |               |                  |               | Between<br>B & C                               | Between<br>A & B |
| 20-29                | 0/2 = 0.0%    | 4/54 = 7.4%      | 1/6 = 16.7%   | —  | —                |
| 30-39                | 3/13 = 23.1%  | 11/143 = 7.7%    | 3/24 = 12.5%  | NS   | NS               |
| 40-49                | 4/9 = 44.4%   | 21/232 = 9.1%    | 3/22 = 13.6%  | NS   | —                |
| 50-59                | 9/17 = 52.9%  | 39/363 = 10.7%   | 3/28 = 10.7%  | NS   | —                |
| 60-69                | 2/5 = 40.0%   | 78/474 = 16.5%   | 0/7 = 0.0%    | —  | —                |
| Total                | 18/46 = 39.1% | 153/1266 = 12.1% | 10/87 = 11.5% | NS   | —                |
| <b>Sex</b>           |               |                  |               |  |                  |
| Male                 | 7/19 = 36.8%  | 60/683 = 8.8%    | 2/50 = 4.0%   | NS   | —                |
| Female               | 11/27 = 40.7% | 93/583 = 16.0%   | 8/37 = 21.6%  | NS   | —                |
| <b>Ethnic Groups</b> |               |                  |               |  |                  |
| Caucasian            | 7/18 = 38.9%  | 110/914 = 12.0%  | 7/59 = 11.9%  | NS   | —                |
| Negro                | 3/10 = 30.0%  | 16/179 = 8.9%    | 0/9 = 0.0%    | —  | —                |
| Spanish American     | 8/18 = 44.4%  | 27/173 = 15.6%   | 3/19 = 15.8%  | NS   | —                |

Note —denotes inadequate sample sizes for statistical tests NS denotes non significance  
denotes significance at the 0.01 level  
denotes significance at the 0.05 level

The autopsy results of two other groups of patients were evaluated Group B consisted of 1,266 rheumatic heart disease cases autopsied at LAC-USC—MC between 1949 and 1973 Group C was a subset of Group B and consisted of 87 patients with severe valvular heart disease who had required surgical repair and/or valve replacement but did not survive valve replacement for a period greater than one month The presence or absence of gallstones was determined in both groups and correlated with their age sex and race The 87 cases in Group C were studied in greater detail to determine the valve(s) that were predominantly affected by the disease process because turbulence often has been cited as a factor leading to intravascular hemolysis Group C was selected for analysis because the degree of turbulence associated with the affected valves of that group probably was less than occurred in Group A but greater than occurred in Group B

The prevalence of gallstones was determined in all three groups and was correlated with age sex, race and the valve site involved

## Results

A diagnosis of rheumatic heart disease was established at autopsy in 2,046 of 46,041 cases surveyed The prevalence of rheumatic heart disease was 44.4 per 1,000 autopsied cases Chole-

lithiasis was present in 301 cases or 14.7 per cent of all rheumatic heart disease cases autopsied here Patients in ethnic groups other than Caucasian, Negro, and Spanish American and those outside the age range 20 to 69 years subsequently were eliminated from the 2,046 rheumatic heart disease cases in order to make direct comparisons with Groups C and A As a result, 1,266 rheumatic heart disease cases (Group B) were eligible for statistical comparison of prevalence of gallstones

**Group A—Heart valve prostheses recipients**  
Table I presents information on prevalence of gallstones for the 46 heart valve prostheses recipients in our study for comparison with the Group B and C results Although the prevalence of gallstones appeared to show a similar progressive increase with age and similar differences between males and females and among ethnic groups, no statistically significant differences were found with respect to age sex and race within this group This is due largely to the relatively small sample of patients in our study In general, the over all prevalence of gallstones in our group of heart valve prostheses recipients is 39.1 per cent which is much higher than either Group B or Group C

**Group B—Rheumatic heart disease group**  
Cholelithiasis was present in 153 of the 1,266 cases

(12.1 per cent) in this group. Table I presents the progressive increase in prevalence of gallstones with advancing age as well as the difference between males and females and ethnic groups. The progressive increase of gallstone prevalence with advancing age and the higher prevalence in females were found to be statistically significant at the 0.01 level. Although the prevalence rate appeared higher in the Spanish American group and was lower in the Negro group, the prevalence rates among ethnic groups were not found to be statistically significant.

**Group C—Severe valvular heart disease group.** All 87 autopsied cases with severe valvular heart disease were eligible for comparison with the study group with respect to age and ethnicity. However, the numbers of patients in the age interval of 20 to 29 years and 60 to 69 years and in the Negro group were relatively small so that comparisons for those age and race classifications were thereby restricted. In this group of 87 selected cases with severe valvular heart disease, ten (11.5 per cent) had cholelithiasis. Table I presents the distributions of the prevalence of gallstones in Group C by age, sex, and race. The differences in prevalence of gallstones among the various age groups and among the three ethnic groups were not found to be statistically significant within this group, but the difference between males and females was significant at the 0.05 level. Due to differences in the distributions of age, sex, and race between this group and Group B, comparisons between them should be made for each classification rather than the entire group as a whole. However, there was no statistically significant difference between Groups B and C in any classification (Table I, second column from the right).

The patients were screened in an outpatient setting for evidence suggestive of hemolysis. All patients were at least three months post operation at the time of the screening. Either a positive urine examination for hemosiderin or a serum haptoglobin of less than 50 mg/ml was found in 41 of the 44 patients (93 per cent) in whom data was available. Random corrected reticulocyte counts were obtained on multiple occasions in 45 patients and were averaged for each patient. The mean corrected reticulocyte count for the total group was  $1.95 \pm 0.79$ . The mean for the 11 patients with gallstones ( $2.19 \pm 1.02$ ) was higher than those without gallstones ( $1.81 \pm 0.58$ ) but a

t test comparison did not reveal a statistically significant difference. Although a mild degree of hemolysis was felt to be present, significant anemia was not a problem in our patient population. The mean hemoglobin for the male patients was  $15.11 \pm 1.39$  Gm/100 ml, and for the female patients was  $13.55 \pm 1.57$  Gm/100 ml. Only three patients had hemoglobins outside of the normal range; none had a hemoglobin of less than 9 Gm/100 ml, and other etiologies for the anemia were present.

Comparisons of prevalence of gallstones were made among the three groups of patients with respect to each classification of age, sex, and race. The prevalence rates as well as the statistical test findings are presented in Table I. Note that the over all prevalence of gallstones in Group B is very close to that of Group C. No significant differences in prevalence of gallstones were found between the rheumatic heart disease patients and the severe valvular heart disease subset. With the exception of the age interval 20 to 29 years, the heart valve prostheses recipients were found to have higher prevalence rates than both the rheumatic heart disease group (Group B) and the severe valvular heart disease group (Group C). Between ages 40 to 49 years, the prevalence rate is about four times higher in the valve prostheses recipients (44.4 per cent compared to 9.1 per cent and 13.6 per cent) and between ages 50 to 59 years it is about five times higher (52.0 per cent compared to 10.7 per cent and 10.7 per cent). The prevalence is almost doubled for females (40.7 per cent compared to 16.0 per cent and 21.6 per cent) and is about four times higher for males (36.8 per cent compared to 8.8 per cent and 4.0 per cent). In all ethnic groups, the over all prevalence of gallstones is about three times greater in the group of valve prostheses recipients.

Our present data enable an exploratory comparison to be made of the prevalence of gallstones with respect to the valve site involved. Table II indicates the prevalence rates for males and females with respect to the valve sites involved for the severe valvular heart patients (Group C) and the heart valve prostheses recipients (Group A). Note that when multiple valves were severely damaged, the lesion was described as being combined. It appears that the prevalence of gallstones in valve recipients (Group A) is higher in the group involving the mitral valve than in the aortic valve group. This

**Table II** Exploratory comparisons of prevalence of gallstones between valve prosthesis recipients (Group A) and severe valvular heart disease patients (Group C) with respect to valve site and sex

| Male                |              |             | Female              |              |              |
|---------------------|--------------|-------------|---------------------|--------------|--------------|
| Involved valve site | Group A      | Group C     | Involved valve site | Group A      | Group C      |
| Aortic              | 5/14 = 35.7% | 1/21 = 4.8% | Aortic              | 2/7 = 28.6%  | 0/6 = 0.0%   |
| Mitral              | 2/4 = 50.0%  | 0/20 = 0.0% | Mitral              | 7/17 = 41.2% | 6/25 = 24.0% |
| Combined            | 0/1 = 0.0%   | 1/9 = 11.1% | Combined            | 2/3 = 66.7%  | 2/6 = 33.3%  |

**Table III** Male/female ratios in various patient groups with and without prosthetic heart valve replacement and comparisons with the literature

| Group             | Reference                          | Total No patients |        |       | No. with gallstones |        |       | Per cent with gallstones |        |       |
|-------------------|------------------------------------|-------------------|--------|-------|---------------------|--------|-------|--------------------------|--------|-------|
|                   |                                    | Male              | Female | Ratio | Male                | Female | Ratio | Male                     | Female | Ratio |
| General autopsy   | Newman and Northup                 | 26 479            | 17 838 | 1.48  | 1914                | 2820   | 0.68  | 7.2                      | 15.8   | 0.46  |
| B                 | This study                         | 683               | 583    | 1.17  | 60                  | 93     | 0.65  | 8.8                      | 16.0   | 0.55  |
| Valve disease     | Merendino and Manhas <sup>17</sup> | 10                | 13     | 0.77  | 1                   | 2      | 0.50  | 10.0                     | 15.4   | 0.65  |
| C                 | This study                         | 50                | 37     | 1.35  | 11                  | 8      | 0.25  | 4.0                      | 21.6   | 0.19  |
| Valve replacement | Merendino and Manhas <sup>17</sup> | 32                | 7      | 4.6   | 10                  | 2      | 5.00  | 31.2                     | 7.6    | 1.09  |
| A                 | This study                         | 111               | 27     | 0.7   | 7                   | 11     | 0.64  | 36.8                     | 40.7   | 0.90  |

fact seems to contradict the general impression that the opposite situation is true.

### Discussion

The data on the prevalence of gallstones presented herein agrees in general with other information published previously. Our Group B data may be compared with the extensive autopsy results of Newman and Northup<sup>18</sup> for gallstone prevalence only their data for Caucasians and Negroes in the United States was considered for this purpose. Such a comparison shows that the rise in gallstone prevalence with age for persons with rheumatic heart disease (Group B) is substantially the same as for the undesignated general population of Newman and Northup. Our Group C data, however indicates a contrasting trend with a decreasing prevalence of gallstones with increasing age beginning in middle age. This effect for patients with valvular heart disease was reported as well by Merendino and Manhas<sup>17</sup> and cannot be readily explained.

Of much interest is the completely different trend that appears in prosthetic heart valve recipients (Group A). A striking increase in gallstone prevalence with age is apparent with a peak occurring in the 50 to 60 year decade. In that decade our prosthetic valve recipients are subject

to a prevalence of gallstones that exceeds Group B and Group C by a factor of five. The reason for this trend is unknown but it may be influenced by the relatively small sample size and thus should be viewed with some reservation. The difference in magnitude however, probably is due to increased red cell destruction and bilirubin production.

A comparison of our results with the data of Merendino and Manhas<sup>17</sup> is pertinent. Their Group II is comparable to our Group A patients with prosthetic heart valve replacement. However the differences should be noted: there are significant differences between our study and their study with respect to male/female ratio, ethnic composition, valve-site involvement and group size. Their study groups were somewhat smaller than ours, and were almost entirely Caucasian. But the major difference is that their prosthetic valve group consisted mostly of male aortic valve recipients whereas nearly 40 per cent of our Group A were female mitral valve recipients. Despite these differences the trend of our data for prevalence of gallstones with age is in agreement with the data of Merendino and Manhas. In absolute magnitude however our prevalence rates are somewhat higher than theirs.

Additional insight may be gained from Table III which summarized the various data with respect to male/female ratio. The last column on the right represents the ratio of percentage of males with gallstones (in a given group) to the percentage of females with gallstones. The values for Groups B and C and corresponding data reflect the frequent observation that the prevalence of gallstones in males is substantially lower than among females. In prosthetic valve recipients (Group A) however it appears that males are about as likely to develop gallstones as females (See also Table I).

The mechanisms of gallstone formation have been discussed in detail elsewhere.<sup>1, 2, 3</sup> Gallstones associated with hemolytic disease have been observed in hereditary spherocytosis<sup>4, 5</sup> and sickle cell anemia.<sup>6</sup> In the case of prosthetic heart valve recipients gallstones are thought to arise from bilirubin production resulting from hemolysis.<sup>7</sup>

Mechanical trauma to red cells in valvular disease and prosthetic replacement frequently has been ascribed to turbulence<sup>8, 9</sup> or excessive fluid shear stresses.<sup>10</sup> The hypothesis of turbulence generated hemolysis would appear to gain credence from the adverse effects of exercise observed in patients with valvular heart disease<sup>11</sup> or in recipients of valve prostheses.<sup>12, 13</sup> However several investigators have expressed doubt that turbulence by itself is a primary cause of mechanical hemolysis.<sup>14, 15</sup> The hypothesis that hemolysis arises mainly from turbulence is probably too simplistic.

It has been shown by Blackshear<sup>16, 17</sup> that extreme shear stresses associated with intense turbulence far greater than might be expected physiologically are required to produce significant hemolysis in blood flowing far distant from surfaces. Turbulence could however influence red cell encounter with surfaces and affect other interfacial phenomena. In the case of paravalvular leaks regurgitation may produce an increased frequency of red cell encounters with surfaces and turbulence may not be the major source of hemolysis. Blackshear and other investigators believe that mechanical hemolysis is due primarily to the interactions of red cells with surfaces.

Two of the 18 patients with gallstones (11 per cent) in Group A subsequently have developed symptoms of cholecystitis requiring cholecystec-

tomy. In neither instance however were the removed stones analyzed for bilirubin content. We do not plan elective cholecystectomy in the other 16 patients at this time because the benefit to risk ratio does not appear to warrant this especially because all of the patients are receiving anticoagulant therapy.

## Conclusions

The results of this study have established that the prevalence of gallstones in patients with heart valve prostheses is significantly greater than in patients with mild or severe valvular heart disease without valve replacement. Apparently the formation of gallstones may result from even mild mechanical hemolysis. Valve prosthesis recipients should be evaluated carefully for symptoms of gallbladder disease at periodic intervals especially late after valve replacement. To further define the problem we recommend that gallstones removed from prosthetic heart valve patients at surgery or at autopsy be analyzed for chemical composition especially to determine the existence of higher than average bilirubin content even in the case of calcium stones.

## Summary

The results of this investigation reveal that 39 per cent of patients in a study group of 46 patients with heart valve prostheses had gallstones if they survived 18 months or longer following valve replacement. In contrast the prevalence of gallstones in a general population of autopsied rheumatic heart disease patients including those who had been operated for severe valvular heart disease and had not survived for more than one month was only 12 per cent. These findings suggest that gallstones are a frequent late complication of heart valve replacement.

The authors are indebted to Jean T. Ikegami, B.S.N. and Ellen Batista, B.S.N., for assistance in assembling, sorting and compiling patient records.

## REFERENCES

1. Yacoub M. H., Rogers K. and Crossland Taylor P. Red cell survival in patients with aortic valve disease. *Thorax* 20: 367, 1965.
2. Miller D. S., Mengel C. E., Kremer W. B., Gutterman J. and Spinninger H. Intravascular hemolysis in a patient with valvular heart disease. *Ann Intern Med* 65: 210, 1966.
3. Forshaw J., and Harwood L. Red blood cell abnormalities in cardiac valvular disease. *J Clin Pathol* 20: 848, 1967.



**Table II** Exploratory comparisons of prevalence of gallstones between valve prosthesis recipients (Group A) and severe valvular heart disease patients (Group C) with respect to valve site and sex

| Male                |              |             | Female              |              |              |
|---------------------|--------------|-------------|---------------------|--------------|--------------|
| Involved valve site | Group A      | Group C     | Involved valve site | Group A      | Group C      |
| Aortic              | 5/14 = 35.7% | 1/21 = 4.8% | Aortic              | 2/7 = 28.6%  | 0/6 = 0.0%   |
| Mitral              | 2/4 = 50.0%  | 0/20 = 0.0% | Mitral              | 7/17 = 41.2% | 6/75 = 24.0% |
| Combined            | 0/1 = 0.0%   | 1/9 = 11.1% | Combined            | 2/3 = 66.7%  | 2/6 = 33.3%  |

**Table III** Male/female ratios in various patient groups with and without prosthetic heart valve replacement and comparisons with the literature

| Group             | Reference                          | Total No patients |        |       | No with gallstones |        |       | Per cent with gallstones |        |       |
|-------------------|------------------------------------|-------------------|--------|-------|--------------------|--------|-------|--------------------------|--------|-------|
|                   |                                    | Male              | Female | Ratio | Male               | Female | Ratio | Male                     | Female | Ratio |
| General autopsy   | Newman and Northup                 | 26 479            | 17 838 | 1.48  | 1914               | 2 820  | 0.68  | 7.2                      | 15.8   | 0.46  |
| B                 | This study                         | 683               | 583    | 1.17  | 60                 | 93     | 0.65  | 8.8                      | 16.0   | 0.55  |
| Valve disease     | Merendino and Manhas <sup>17</sup> | 10                | 13     | 0.77  | 1                  | 2      | 0.50  | 10.0                     | 13.4   | 0.66  |
| C                 | This study                         | 50                | 37     | 1.35  | 2                  | 8      | 0.25  | 4.0                      | 21.6   | 0.19  |
| Valve replacement | Merendino and Manhas <sup>17</sup> | 32                | 7      | 4.6   | 10                 | 2      | 5.00  | 31.2                     | 28.6   | 1.09  |
| A                 | This study                         | 19                | 27     | 0.7   | 7                  | 11     | 0.64  | 36.8                     | 40.7   | 0.90  |

fact seems to contradict the general impression that the opposite situation is true

## Discussion

The data on the prevalence of gallstones presented herein agrees in general with other information published previously. Our Group B data may be compared with the extensive autopsy results of Newman and Northup<sup>19</sup> for gallstone prevalence, only their data for Caucasians and Negroes in the United States was considered for this purpose. Such a comparison shows that the rise in gallstone prevalence with age for persons with rheumatic heart disease (Group B) is substantially the same as for the undesignated general population of Newman and Northup. Our Group C data, however, indicates a contrasting trend with a decreasing prevalence of gallstones with increasing age beginning in middle age. This effect for patients with valvular heart disease was reported as well by Merendino and Manhas<sup>17</sup> and cannot be readily explained.

Of much interest is the completely different trend that appears in prosthetic heart valve recipients (Group A). A striking increase in gallstone prevalence with age is apparent, with a peak occurring in the 50 to 60 year decade. In that decade our prosthetic valve recipients are subject

to a prevalence of gallstones that exceeds Group B and Group C by a factor of five. The reason for this trend is unknown but it may be influenced by the relatively small sample size, and thus should be viewed with some reservation. The difference in magnitude however probably is due to increased red cell destruction and bilirubin production.

A comparison of our results with the data of Merendino and Manhas<sup>17</sup> is pertinent. Their Group B is comparable to our Group A patients with prosthetic heart valve replacement. However, the differences should be noted: there are significant differences between our study and their study with respect to male/female ratio, ethnic composition, valve-site involvement, and group size. Their study groups were somewhat smaller than ours and were almost entirely Caucasian. But the major difference is that their prosthetic valve group consisted mostly of male aortic valve recipients whereas nearly 40 per cent of our Group A were female mitral valve recipients. Despite these differences the trend of our data for prevalence of gallstones with age is in agreement with the data of Merendino and Manhas<sup>17</sup>. In absolute magnitude, however, our prevalence rates are somewhat higher than theirs.

# The influence of atrial systole on ventricular capture by failing artificial pacemakers II

## Experimental observations

William S Abernathy MD  
Gregory H Ferner Ph D  
Gordon K Moe MD Ph D  
Utica N Y

The efficacy of ventricular capture by failing artificial pacemakers can be influenced by atrial activity. Twenty six cases have been reviewed recently. Two hypotheses have been advanced to explain this phenomenon. One theory invokes an electrotonic interaction (Wedensky facilitation or inhibition) between the pacemaker stimulus and the atrial depolarization (The Wedensky effect is a separate phenomenon and is not considered in this report). The other theory postulates that atrial systole influences the efficacy of capture by altering the physical contact between the pacing electrode and the ventricular myocardium. The present study was undertaken to reproduce this phenomenon in the dog and to ascertain which of these two mechanisms was operative. The results strongly support the mechanical hypothesis.

### Methods

Mongrel dogs of either sex weighing 10 to 23 kilograms were anesthetized with sodium pentobarbital (30 mg/Kg intravenously) and given additional doses as required. Following a right thoracotomy the heart was suspended in a pericardial cradle. In some dogs the right upper lobe of the lung was excised to facilitate exposure. A Harvard respirator provided ventilation. Atrioventricular block was created in one of

two ways. The ends of two pieces of fine (0.005 inch diameter) Teflon coated steel wire were bent to form hooks and were inserted through the right atrial wall into the region of the His bundle. After recording a His bundle electrogram to verify the position, a strong electric shock (20 to 150 joules) was passed through the heart using both wires as one pole and a large (8.7 cm diameter) metal paddle applied to the left ventricle as the other pole. Complete heart block was achieved in six dogs and first degree block ( $AV = 139$  to  $149$  msec) in one dog. Complete heart block was produced in an additional five dogs by injecting formalin into the His bundle.

The mid right atrium was paced through a close bipolar epicardial electrode. The right ventricle was stimulated through a transvenous bipolar pacing catheter (USCI No 007152) the position of this catheter in the right ventricle was adjusted by trial and error until atrial systole exerted an influence on the test stimulus. All stimuli were of 2 msec duration and were passed through isolation transformers. The strength of all stimuli except the ventricular test stimulus ( $V_s$ ) was two to three times threshold.

Fig 1 illustrates the stimulation patterns employed in this study. The atrium and ventricle were sequentially paced with a delay of 100 msec and with a train of 9 to 20 (usually 10) basic stimuli. In Fig 1 the last of these are designated  $As_n$ ,  $Vs_n$ ,  $As_n$ ,  $Vs_n$ . (Stimuli are denoted by the subscript "n" and the corresponding beats are designated without the subscript for example stimulus  $As_n$  gives rise to beat  $A_n$ ). In any given experiment the cycle length of the basic stimuli

From the Masonic Medical Research Laboratory, Utica, N.Y.  
Supported in part by grant HL-19487 from the National Heart, Lung, and Blood Institute.  
Received for publication Sept. 23, 1977.  
Accepted for publication Nov. 17, 1977.  
Reprint requests: William S. Abernathy, MD, Masonic Medical Research Laboratory, Utica, N.Y. 13503.

- 4 Eyster M, Mayer K and McKenzie S Traumatic hemolysis with iron deficiency in patients with aortic valve lesions *Ann Intern Med* 68:995, 1968
- 5 Wallace H W, Kenepp D L and Blakemore W S Quantitation of red cell destruction associated with valvular disease and prosthetic valves *J Thorac Cardiovasc Surg* 60:842, 1970
- 6 Brodeur M T H, Sutherland C W, Kohler R D, Starr A, Kimsey J A and Grunsold II E Red blood cell survival in patients with aortic valve disease and ball valve prostheses *Circulation* 32:570, 1965
- 7 Walsh J H, Starr A and Ritzmann L W Intravascular hemolysis in patients with prosthetic valves and valvular heart disease *Circulation* 39 and 40 (Suppl I) 1:135, 1969
- 8 Rogers B M and Sabiston D C Hemolytic anemia following prosthetic valve replacement *Circulation* 39 and 40 (Suppl I) 1:155, 1969
- 9 Crexells C, Aeschlde N, Bonny Y, Lepage G and Campeau L Factors influencing hemolysis in valve prostheses *AM HEART J* 81:161, 1972
- 10 Bernstein, E F Certain aspects of blood interfacial phenomena—Red blood cells *Fed Proc Fed Am Soc Exp Biol* 30:1510, 1971
- 11 Garcia M C, Clarysse A M, Alexander C S, Sako Y and Swaim W R Hemolytic anemia due to progressive enlargement of silastic ball component of aortic prostheses *Circulation* 38:505, 1968
- 12 Eyster E Traumatic hemolysis with hemoglobinuria due to ball variance *Blood* 33:391, 1969
- 13 Allen P and Robertson R The significance of intermittent regurgitation in aortic valve prostheses *J Thorac Cardiovasc Surg* 54:549, 1967
- 14 Stevenson T D and Baker H J Hemolytic anemia following insertion of Starr Edwards valve prosthesis *Lancet* 2:982, 1964
- 15 Herr R, Starr A, McCord C W and Wood J A Special problems following valve replacement—Embolus leak infection, red cell damage *Ann Thorac Surg* 1:403, 1965
- 16 Kastor J A, Akabarian M, Buckley M J, Dinsmore R E, Sanders C A, Scannell J E and Austen, W G Paravalvular leaks and hemolytic anemia following insertion of Starr Edwards aortic and mitral valves, *J Thorac Cardiovasc Surg* 56:279, 1968
- 17 Merendino K A and Manhas D R Man made pill stones—A new entity following cardiac valve replacement *Ann Surg* 177:694, 1973
- 18 Glenn F and Redo S F Mitral stenosis and gallstones, *Ann Surg* 147:817, 1958
- 19 Newman H F and Northup J D The autopsy incidence of gallstones *Surg Gynecol Obstet Internat. Abstracts Surg* 109:1, 1959
- 20 Small D M Gallstones—Current concepts *New Engl J Med* 279:588, 1968
- 21 Womack M A The development of gallstones, *Surg Gynecol Obstet* 133:937, 1971
- 22 Young L E, Izzo M J and Platzer R F Hereditary spherocytosis I. Clinical, hematologic and genetic features in 28 cases with particular reference to the osmotic and mechanical fragility of incubated erythrocytes *Blood* 6:1073, 1951
- 23 Bates G C and Brown C H Incidence of gallbladder disease in chronic hemolytic anemia (spherocytosis) *Gastroenterology* 21:104, 1959
- 24 Barrett Connor E Cholelithiasis in sickle cell anemia *Am J Med* 45:889, 1968
- 25 DeCesare W, Rath C and Hufnagel C Hemolytic anemia of mechanical origin with aortic valve prostheses, *N Engl J Med* 272:1045, 1965
- 26 Blackshear P L Mechanical hemolysis in flowing blood, chapt 19 in *Biomechanics—its foundations and objectives* edited by Klug Y C, Perrone N and Anliker M, Englewood Cliffs New Jersey, 1977 Prentice Hall Inc p 501
- 27 Blackshear P L Hemolysis at prosthetic surfaces, Chapt 11 in *The chemistry of biosurfaces* vol. 2 edited by Hair M L, New York 1972 Marcel Dekker p 512

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following statement, signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company, in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

delivered at the end of expiration. This was accomplished by matching the number and cycle length of the basic stimuli to the respiratory rate. The timing was checked by means of an electrical signal elicited from the respirator at the onset of inspiration.

In all experiments a standard lead electrocardiogram, a close bipolar mid right atrial electrogram, the ventricular stimuli, and the respiratory signal were recorded. The A-Vs interval was measured from the intrinsic deflection of the atrial electrogram to the test stimulus. The A-A interval was measured from one intrinsic deflection to the other. The capture by Vs was judged by examining the electrocardiogram for the presence or absence of a QRS immediately following Vs.

Right atrial pressure was measured through a transvenous catheter or through a large bore (4.5 mm internal diameter) copper tube inserted in the right atrial appendage. These were connected to a Statham transducer (model P23BC) interfaced with an Electronics for Medicine amplifier (model SGA). The transducer was calibrated against a mercury manometer. All pressures were measured at the time Vs occurred and were measured to the nearest 0.5 or 1.0 mm Hg.

All data were recorded on a TEAC tape recorder (model R 351 F) and were later photographed on continuously moving (25 mm/sec) film with a Grass Kymograph camera (model C4 K). The photographic image was enlarged and the data were measured with an accuracy of at least  $\pm 5$  msec. Time calibrations were provided both by a digital interval generator (built by W. J. Mueller) and by a Tektronix interval generator (model 180A).

The statistical tests used were Chi squared derived from a contingency table with Yates correction where appropriate, Student's *t* test for the difference of the means, and the Wilcoxon two sample test for the unpaired case.

## Results

**Facilitation and inhibition of Vs.** Facilitation of ventricular capture by Vs is illustrated in Fig. 2. In the control state (Fig. 2A) Vs did not excite the ventricle when As was omitted, and an atrial escape beat (AE) occurred after Vs. In the test condition (Fig. 2B) Vs captured the ventricle when a single atrial beat (A) preceded Vs by 88 msec. Note that the right atrial pressure coincident with Vs was low in the absence of A (Fig.

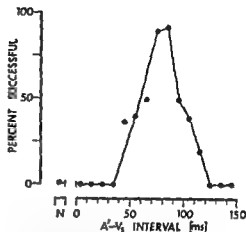


Fig. 3 Facilitation of Vs. Abscissa: the A-Vs interval in msec. Data are plotted in 10 msec groups, i.e., 0 to 10, 11 to 20, 21 to 30, etc. 'N' refers to data collected when As was omitted, and an atrial escape beat (AE) occurred after Vs. Ordinate: the percent of Vs that was successful in ventricular capture at any given A-Vs interval. Total number of Vs = 666. Experiment performed on Apr. 14, 1977.

2A) and high in the presence of A' (Fig. 2B). The time course of facilitation was examined by placing A at various times before Vs. The results of one such experiment are shown in Fig. 3. When the A-Vs interval was less than 41 msec or greater than 110 msec, Vs did not excite the heart. However, when the A-Vs interval was 41 to 110 msec, A facilitated ventricular capture by Vs. Inhibition of ventricular capture was demonstrated in other experiments of the same design. In six dogs, either facilitation or inhibition of ventricular capture could be alternatively elicited by changing the position of the pacing catheter in the ventricle; an example of this is presented in Fig. 4, in which all of the data are from the same dog. In this figure, A facilitated Vs when the A-Vs interval was 51 to 140 msec, and A inhibited Vs when the interval was 61 to 170 msec. In most experiments, A affected the efficacy of Vs when the A-Vs interval was 41 to 150 msec; the narrowest effective range observed was 31 to 110 msec, and the widest effective range was 11 to 160 msec. Faster basic driving rates tended to give narrower ranges of effective A-Vs intervals, but this observation was not systematically examined.

Experiments in which the efficacy of Vs was influenced by a single atrial beat (A) were performed in 11 dogs; facilitation was shown in seven and inhibition in eight. Eleven complete curves similar to those shown in Figs. 3 and 4 were constructed from these experiments.

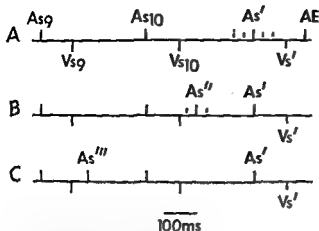


Fig 1 Stimulation patterns. Vertical lines above and below the horizontal line represent stimuli delivered to the atrium and ventricle respectively. The strength of the test stimulus ( $V_s$ ) was less than that of the basic stimuli ( $V_s$   $V_{s10}$ ). The broken lines in panels A and B indicate that  $As$  and  $As'$  may assume various temporal positions. Time calibration = 100 msec

was constant, the cycle lengths of all the experiments varied between 220 and 380 msec (mean = 323 msec). A ventricular test stimulus ( $V_s'$ ) was then delivered at approximately the same interval as the basic stimuli, the test stimulus was never premature enough to encroach upon a possible zone of supernormal excitability. The purpose of this test stimulus ( $V_s'$ ) was to imitate a failing pacemaker, hence, the strength of  $V_s'$  was adjusted to a value that was barely successful or barely unsuccessful in exciting the heart.

The influence of atrial systole on the efficacy of  $V_s'$  was studied by introducing one or more atrial stimuli ( $As$ ,  $As'$ ,  $As'''$ ) as illustrated in Fig 1. The influence of atrial systole on  $V_s'$  was demonstrated as follows. In the control situation no atrial stimulus was delivered before  $V_s'$ , and an atrial escape beat (AE) occurred after  $V_s'$  (Fig 1A). In the test situation, a single atrial stimulus ( $As'$ ) was delivered at a variable interval before  $V_s'$  (Fig 1A). The phenomenon under study was present when a suitably timed atrial beat ( $A'$ ) changed the excitatory efficacy of  $V_s'$  as compared to control (no  $As$ ).

The mechanism of this phenomenon was investigated by altering the hemodynamic performance of the atrial beat ( $A'$ ) immediately preceding  $V_s'$ . The purpose of these experiments was to dissociate partially the hemodynamic and electrotonic effects of  $A'$ . Fig 1B shows a sequence that decreased the strength of the contraction of  $A'$  as reflected by the right atrial pressure. Holding  $As$  in a fixed temporal position another atrial stimulus ( $As'$ ) was interpolated at various times after the last basic beat (Fig 1B). In other

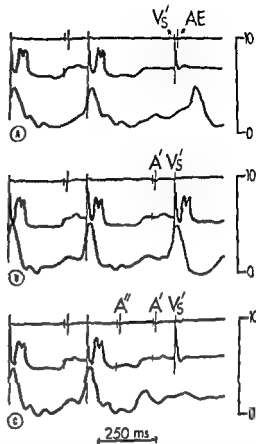


Fig 2 Facilitation of  $V_s$  and interpolation of A. In each panel top line = atrial electrogram; middle line = electrocardiogram; bottom line = right atrial pressure. Panel A control. Panel B facilitation ( $A$   $V_s$  = 85 msec;  $A'$  = 157 msec). The figures were traced from original photographs. The records of the ventricular stimuli were omitted. Time calibration (below) = 250 msec. Pressure calibrations (right) = 0 to 10 mm Hg. Experiment performed on March 2, 1977.

experiments, the contraction of  $A'$  was enhanced by interpolating an atrial stimulus ( $As'$ ) in the penultimate diastole (Fig 1C). The position of  $As'''$  was held constant, and the position of  $As$  was usually, but not always, fixed.

That the excitatory efficacy of  $V_s$  was in fact being influenced by  $A'$  was verified repeatedly. After at most every tenth  $V_s$ , the atrial stimulation sequence was changed in such a way that the efficacy of  $V_s$  should change too. For example, if  $V_s'$  excited the ventricle with  $A'$  preceding  $V_s'$  by 100 msec, then non capture by  $V_s'$  in the absence of  $A'$  was confirmed regularly. Data were accepted for analysis only if such a reversal of effect occurred within four test cycles.

Early in the study it became apparent that respiration had an independent effect on the efficacy of  $V_s$ . This effect was characterized by failure of capture on inspiration and was probably caused by movement of the heart or catheter. To compensate for this respiratory effect all  $V_s$  were

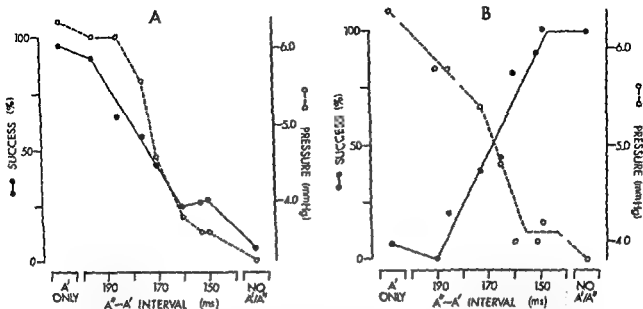


Fig 6 Facilitation (panel A) and inhibition (panel B) of  $V_s$  and interpolation of A (both panels) Abscissa: NO A/A control A ONLY first test condition A A INTERVAL sec and test condition the time interval in msec. between these beats Left ordinate (●) the per cent of  $V_s$  that was successful in ventricular capture at any given stimulation pattern Right ordinate (○) the arithmetic average of all the right atrial pressures recorded during any given stimulation pattern In these experiments, the A  $V_s$  interval was constant at 100 msec until the A A interval fell below 160 msec, at which point the A  $V_s$  interval was 85 to 100 msec Total number of  $V_s$  = 687 (panel A) and 431 (panel B) Experiment performed on March '8 1977

aberrant or if the A  $V_s$  interval shortened by more than 15 msec as compared to the initial test condition (A ONLY) In all dogs studied with an interpolated A a reduction of the pressure generated by A and a nullification of the effect of A on  $V_s$  were seen at A A intervals which produced no aberration of A and no change in the A  $V_s$  interval

**Interpolation experiments with enhancement of the contraction of A** In some experiments the control condition was that the efficacy of  $V_s$  was not influenced by the presence the timing (A  $V_s$  interval) or the absence of A alone (Fig 7A) However when an atrial beat (A) was interpolated in the penultimate cycle the hemodynamic force of A was enhanced and A then exerted an effect on the efficacy of  $V_s$  (Fig 7B) In Fig 7A the atrial pressure at the time of  $V_s$  was the same as during the basic beats and  $V_s$  did not excite the ventricle In Fig 7B interpolation of A caused an increase in the pressure generated by A and A then facilitated  $V_s$  The change in the efficacy of  $V_s$  was not due solely to the presence of A This was demonstrated in three dogs by changing the A  $V_s$  interval while leaving A in a fixed position (not illustrated)  $V_s$  was influenced

only during a specific range of A  $V_s$  intervals (40 to 150 msec)

The results of all the experiments of this type are summarized in Table I (Experiments with a variable A  $V_s$  interval are excluded) In all dogs interpolation of A significantly increased the pressure generated by A' and the hemodynamically enhanced A then significantly changed the efficacy of  $V_s$

**Atrial pressure and efficacy of  $V_s$**  There was an excellent correlation between the level of the atrial pressure (coincident with  $V_s$ ) and the efficacy of  $V_s$  (Fig 8) An increasing pressure was associated with greater facilitation or greater inhibition of  $V_s$  by A Moreover the correlation between pressure and success (Fig 8) was independent of the stimulation pattern employed An increase in pressure was accomplished by an atrial systole (A) alone with suitable timing (A  $V_s$  intervals of approximately 40 to 150 msec) by hemodynamically enhancing A with an interpolated beat (A) or by an A with a long A A interval A decrease in pressure was achieved by omitting As so that an escape beat occurred after  $V_s$  by relatively short or long A  $V_s$  intervals or by interpolating a beat (A) at a suitable interval

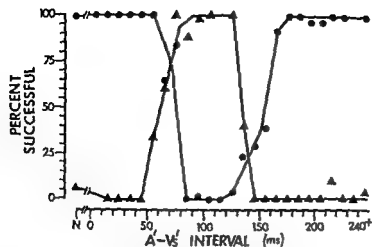


Fig 4 Alternate facilitation and inhibition of Vs in the same dog. Abscissa and ordinate are identical to those in Fig 3 (A). Facilitation total number of Vs = 393 (●) Inhibition total number of Vs = 863. Experiment performed on Mar 29 1977

**Interpolation experiments with weakening of the contraction of A'** In Fig 2B A' facilitated Vs'. When an atrial beat (A'') was interpolated immediately before A', the facilitation was abolished, and Vs' did not excite the ventricle (Fig 2C). Another experiment of this type, but with opposite conditions, is shown in Fig 5. In the control state (not illustrated), A' and A'' were omitted, and Vs excited the ventricle. In Fig 5A, A' alone inhibited ventricular capture by Vs. However, when both A' and A'' were present (Fig 5B), the inhibition disappeared and Vs' again excited the ventricle. In both experiments interpolation of A' did not change the appearance of A' on the electrocardiogram or electrogram, but this interpolation did impair greatly the hemodynamic performance of A' as revealed by the lower pressure at the time Vs occurred (compare Figs 2B and 2C, and Figs 5A and 5B). Fig 5C confirms that A' was hemodynamically ineffective in Fig 5B.

Gradations in the extent of hemodynamic impairment of A' were produced by varying the A'' A' interval while holding the position of A' constant. Fig 6 illustrates the results of two such experiments. In Fig 6A in the control state (NO A' A'') the atrial pressure was low, and Vs did not excite the ventricle. In the first test condition (A' ONLY), the pressure was high and Vs captured the ventricle. When A'' was interpolated at progressively shorter A' A' intervals (A' A' INTERVAL), the atrial pressure generated by A' fell toward the control value and the facilitation of Vs' by A' was progressively eliminated. Following a change in the position of the pacing

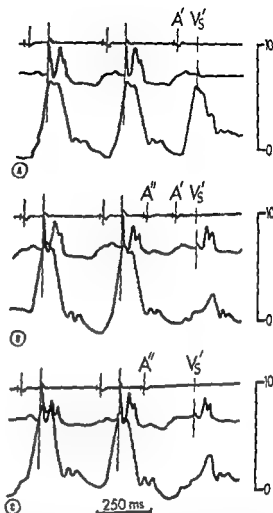


Fig 5 Inhibition of Vs and interpolation of A''. Data records and calibrations are the same as in Fig 2. Panel A inhibition (A' Vs = 95 msec). Panel B interpolation of A' (A Vs = 95 msec A' A' = 132 msec). Panel C A alone (A Vs = 227 msec). Traced from the original photographs. Experiment performed on March 2 1977

catheter, the data in Fig 6B were obtained from the same dog that was represented in Fig 6A. Interpolating A'' at decreasing A'' A' intervals resulted in a progressive loss of the inhibition of Vs' by A' and a progressive fall in the atrial pressure toward the control value (Fig 6B). In both Figs 6A and 6B at short A'' A' intervals the hemodynamic effect of A' became negligible and the efficacy of Vs approached that seen in the absence of both A'' and A'. Moreover, the magnitude of the influence of A' varied directly with the pressure generated by A'.

Experiments of this type were done in five dogs, facilitation was reversed in four and inhibition in four. Seven complete curves of the kind shown in Fig 6 were constructed from the data.

At very short A' A'' intervals (< 150 msec) either A' failed to excite the atrium or the A' A' latency increased and A' became grossly aberrant. Data were rejected from analysis if A' was

Table 1 Summary of the experiments in which interpolation of A<sup>+</sup> enhanced the hemodynamic performance of A

| Date of experiment  | A absent               |                      | A present              |                      | Absent vs present |
|---------------------|------------------------|----------------------|------------------------|----------------------|-------------------|
|                     | Per cent Vs successful | Average RAP $\pm$ SD | Per cent Vs successful | Average RAP $\pm$ SD | p value           |
| <b>Facilitation</b> |                        |                      |                        |                      |                   |
| 4/15/77             | 00 (0/24)              | 43 $\pm$ 03          | 80 (41/51)             | 55 $\pm$ 03          | < 0.001           |
| 5/3/77              | 11 (13/117)            | 45 $\pm$ 05          | 92 (91/99)             | 62 $\pm$ 07          | < 0.001           |
| 5/4/77              | 06 (2/35)              | 45 $\pm$ 03          | 88 (31/33)             | 48 $\pm$ 05          | < 0.01            |
|                     |                        |                      |                        |                      | < 0.001           |
| <b>Inhibition</b>   |                        |                      |                        |                      |                   |
| 4/15/77             | 98 (64/65)             | 55 $\pm$ 05          | 17 (18/109)            | 63 $\pm$ 07          | < 0.001           |
| 5/3/77              | 19 (136/173)           | 58 $\pm$ 05          | 04 (6/136)             | 85 $\pm$ 07          | < 0.001           |
| 5/5/77              | 89 (150/169)           | —                    | 06 (9/143)             | —                    | < 0.001           |

First three horizontal rows = facilitation; last three horizontal rows = inhibition of V<sub>s</sub>

Symbols and abbreviations: A<sup>+</sup> absent = control; A<sup>+</sup> present = test condition, both A and A<sup>+</sup> present. The A<sup>+</sup> interval was constant in each experiment. Per cent Vs successful = the per cent of V<sub>s</sub> that was successful in ventricular capture under the conditions specified. Number in parentheses are the actual number of V<sub>s</sub> successful of the number tested. Average RAP = the arithmetic average of all the right atrial pressures (RAP) recorded under the conditions specified. SD = standard deviation. Absent vs present = statistical comparison of the efficacy of V<sub>s</sub> at the pressure data in the two conditions. p value = the result of testing efficacy with the Chi square test, and of testing the pressure data with the Chi square test, the Student's t test, and the Wilcoxon z value. For each experiment every statistical test gave p < 0.001 except for the experiment of May 4 1977 in which the Chi square test and Student's t test for pressure data gave p < 0.01.

that atrial systole caused motion of the pacing catheter in eight patients

**Interpolation experiments** In order to study these two hypotheses the present experiments were designed to dissociate partially the mechanical and electrotonic effects of the atrial beat (A<sup>+</sup>) immediately before the test stimulus (V<sub>s</sub>). Interpolation of an atrial beat (A<sup>+</sup>) immediately before A resulted in a decrease in the hemodynamic performance of A<sup>+</sup> and conversely interpolation of a beat (A<sup>+</sup>) in the penultimate cycle resulted in an increase in the pressure generated by A. Two observations support the idea that dissociation was achieved. First the configuration of A on the electrocardiogram and atrial electrogram was unchanged after interpolation despite a significant change in the pressure generated by A. Second interpolation of A<sup>+</sup> or A undoubtedly caused some shortening of the action potentials of A as a result of the abrupt increase in atrial rate. However the mechanical effects changed in opposite directions (increase or decrease in pressure) in the two types of interpolation experiments while the electrical effects changed in the same direction (shortening of the action potentials).

These experiments showed that an atrial depolarization by itself was insufficient to alter the efficacy of capture by the ventricular test stimulus (V<sub>s</sub>). This was especially apparent in the mechanical enhancement experiments in which

the normal atrial beat (A<sup>+</sup>, control condition) did not affect the efficacy of the test stimulus (V<sub>s</sub>).

**Atrial pressure** The enhancement or depression of hemodynamic performance seen in the interpolation experiments is a manifestation of the phenomenon of restitution<sup>4</sup> and may be studied in terms of changes in pressure. However it almost certainly was not the atrial pressure itself that affected the efficacy of the test stimulus. Proof that the changes in efficacy were caused by motion of the pacing catheter and/or ventricular myocardium and proof that this motion was caused by atrial systole could have been obtained by measuring the movements of these structures. Technical limitations prevented such measurements. Nevertheless the pressure measurements did verify the changes in hemodynamic performance did correlate well with the changes in efficacy of the test stimulus (Fig 8 and Table 1) and did show that the atrial influence was mediated by a mechanical mechanism.

**Episcardial pacing** In an earlier study using right ventricular epicardial electrodes Arbel and colleagues<sup>5</sup> observed that a suitably timed atrial beat increased the efficacy of capture by a low voltage stimulus. This preliminary report was based on a single experiment conducted in a dog without atrioventricular block. It might be argued that this observation is incompatible with the mechanical hypothesis since the stimulus was



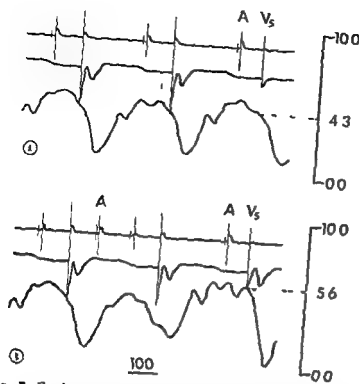


Fig 7 Facilitation of  $V_s$  when the contraction of A was enhanced by interpolation of A. Data records are the same as in Fig 2 Panel A control Panel B interpolation of A.  $A V_s = 75$  msec in both panels. The right atrial pressures coincident with  $V_s$  are indicated by the numbers at the ends of the broken lines. Traced from the original photographs. Time calibration (below) = 100 msec. Pressure calibrations (right) = 0.0 to 100 mm Hg. Experiment performed on April 15 1977.

immediately before  $A'$ . For example the data in Fig 8 came from experiments in one dog in which  $A'$  alone was present at varying  $A V_s$  intervals, in which A was present with varying  $A''-A'$  intervals, and in which  $A_s$  was omitted. In total, 10 correlations of the type shown in Fig 8 were obtained in the six dogs in which technically adequate pressures were recorded.

**The strength of  $V_s$ .** When the strength of  $V_s$  was increased or decreased beyond the value that was barely successful or unsuccessful in ventricular capture A ceased to exert any influence on  $V_s$  regardless of the stimulation pattern used. With reductions in strength all  $V_s$  failed with increases all succeeded.

## Discussion

These experiments have shown that a suitably timed atrial systole can frequently and consistently alter the efficacy of ventricular capture by a low voltage stimulus delivered to the right ventricular endocardium through a bipolar pacing catheter. The results support the idea that this phenomenon is mediated by the mechanical effects of the atrial beat. Without changing the

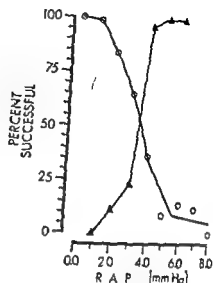


Fig 8 Atrial pressure and efficacy of  $V_s$ . Abscissa right atrial pressure (RAP) in mm Hg. Ordinate the per cent of  $V_s$  (occurring at any given level of pressure) that was successful in ventricular capture (Δ). Facilitation total number of  $V_s = 303$  (○) Inhibition total number of  $V_s = 566$ . Experiment performed on March 2 1977.

appearance or timing of the atrial depolarization weakening of the contraction abolishes a pre-existing atrial influence, and enhancement of the contraction establishes an influence where none existed before.

**Electrotonic hypothesis.** Most earlier reports favored an electrotonic mechanism as the explanation for the influence of atrial activity on the efficacy of pacemaker capture. This hypothesis has been reviewed and analyzed recently.<sup>1</sup> It is very unlikely that an electrotonic mechanism was operative in the experiments described here because of the distance separating the atria and the pacing electrode. Because the space constant of the myocardium is very short,<sup>2</sup> an electrotonic current originating in the atria would be virtually extinguished before it reached the electrode in the right ventricle.

**Mechanical hypothesis.** Several authors have acknowledged the possibility of a mechanical explanation, but few have favored it.<sup>3</sup> This hypothesis proposes that atrial systole alters the efficacy of capture by increasing or decreasing the contact between the electrode tip and the ventricular myocardium. An atrial contraction could move the intra atrial portion of the catheter if the catheter were in close proximity to the atrial wall. Alternatively, by augmenting left ventricular diastolic volume atrial systole could move the ventricular wall relative to the catheter. This hypothesis has received some support from the report of Preston<sup>4</sup> who radiographically observed

Table 1 Summary of the experiments in which interpolation of A enhanced the hemodynamic performance of A

| Date of experiment  | A absent               |                      | A present              |                      | Absent vs present |
|---------------------|------------------------|----------------------|------------------------|----------------------|-------------------|
|                     | Per cent Vs successful | Average RAP $\pm$ SD | Per cent Vs successful | Average RAP $\pm$ SD | p value           |
| <b>Facilitation</b> |                        |                      |                        |                      |                   |
| 4/15/77             | 00 (0/24)              | 43 $\pm$ 03          | 80 (41/51)             | 55 $\pm$ 03          | < 0.001           |
| 5/3/77              | 11 (13/117)            | 45 $\pm$ 05          | 92 (91/99)             | 62 $\pm$ 07          | < 0.001           |
| 5/4/77              | 06 (2/35)              | 45 $\pm$ 03          | 94 (31/33)             | 48 $\pm$ 05          | < 0.01            |
|                     |                        |                      |                        |                      | < 0.001           |
| <b>Inhibition</b>   |                        |                      |                        |                      |                   |
| 4/15/77             | 00 (0/65)              | 55 $\pm$ 05          | 17 (18/109)            | 63 $\pm$ 07          | < 0.001           |
| 5/3/77              | 79 (136/173)           | 58 $\pm$ 05          | 04 (6/136)             | 80 $\pm$ 07          | < 0.001           |
| 5/5/77              | 89 (150/169)           | —                    | 06 (9/143)             | —                    | < 0.001           |

First three horizontal rows = facilitation of Vs. Last three horizontal rows = inhibition of Vs. Symbols and abbreviations: A = absent, A = present, A = absent, A = present. The A Vs interval was constant in each experiment. Per cent Vs successful = the per cent of Vs that was successful in ventricular capture under the conditions specified. Numbers in parentheses are the actual number of Vs successful and the number tested. Average RAP = the arithmetic average of all the right atrial pressures (RAP) recorded under the conditions specified. SD = standard deviation. Absent vs present = statistical comparison of the efficacy of A and the pressure data in the two conditions. p value = the result of the t test, the Chi squared test, and of testing the pressure data with the Chi squared test, the Student's t test, and the Wilcoxon's value. For the experiment very statistical test, p < 0.001, except for the experiment of May 4, 1977 in which the Chi squared test and Student's t test for pressure difference, p < 0.01.

that atrial systole caused motion of the pacing catheter in eight patients.

**Interpolation experiments.** In order to study these two hypotheses the present experiments were designed to dissociate partially the mechanical and electrotonic effects of the atrial beat (A) immediately before the test stimulus (Vs). Interpolation of an atrial beat (A) immediately before A resulted in a decrease in the hemodynamic performance of A and, conversely interpolation of a beat (A) in the penultimate cycle resulted in an increase in the pressure generated by A. Two observations support the idea that dissociation was achieved. First the configuration of A on the electrocardiogram and atrial electrogram was unchanged after interpolation despite a significant change in the pressure generated by A. Second interpolation of A or A undoubtedly caused some shortening of the action potentials of A as a result of the abrupt increase in atrial rate. However the mechanical effects changed in opposite directions (increase or decrease in pressure) in the two types of interpolation experiments while the electrical effects changed in the same direction (shortening of the action potentials).

These experiments showed that an atrial depolarization by itself was insufficient to alter the efficacy of capture by the ventricular test stimulus (Vs). This was especially apparent in the mechanical enhancement experiments in which

the normal atrial beat (A control condition) did not affect the efficacy of the test stimulus (Vs).

**Atrial pressure.** The enhancement or depression of hemodynamic performance seen in the interpolation experiments is a manifestation of the phenomenon of restitution<sup>1</sup> and may be studied in terms of changes in pressure. However it almost certainly was not the atrial pressure itself that affected the efficacy of the test stimulus. Proof that the changes in efficacy were caused by motion of the pacing catheter and/or ventricular myocardium and proof that this motion was caused by atrial systole could have been obtained by measuring the movements of these structures. Technical limitations prevented such measurements. Nevertheless the pressure measurements did verify the changes in hemodynamic performance did correlate well with the changes in efficacy of the test stimulus (Fig 8 and Table 1) and did show that the atrial influence was mediated by a mechanical mechanism.

**Epicardial pacing.** In an earlier study using right ventricular epicardial electrodes Arbel and colleagues observed that a suitably timed atrial beat increased the efficacy of capture by a low voltage stimulus. This preliminary report was based on a single experiment conducted in a dog without atrioventricular block. It might be argued that this observation is incompatible with the mechanical hypothesis since the stimulus was

delivered through epicardial electrodes. However, the mechanical hypothesis does not require gross changes in the electrode contact, depending on the type of epicardial electrode used small changes in contact could result from atrial systole.

In the present study, using a close bipolar electrode firmly hooked into the right ventricular epicardium, we were unable to show that atrial systole had any effect on the efficacy of the test stimulus (Vs'). These experiments were done in three dogs with and without atrioventricular heart block. In those dogs with heart block, the stimulation pattern employed was the one illustrated in Fig. 1A, in the dogs without heart block, the pattern employed was the one used by Arbel and associates.<sup>9</sup> In contrast, in every dog adequately studied with a bipolar endocardial pacing catheter it was possible to show either inhibition or facilitation of the test stimulus by atrial systole.

These results are consistent with the human case reports. In 19 of the 20 cases in which sufficient information is available the pacing catheter was of the transvenous endocardial type.<sup>1</sup> In the single case with an epicardial electrode, the catheter tip had migrated and was not securely fixed to the heart. Thus both the experimental and clinical observations provide additional indirect support for the mechanical hypothesis.

**Clinical implications.** These experimental results combined with the radiographic observations of Preston<sup>6</sup> and the analysis indicating the applicability of the mechanical mechanism to the human cases<sup>1</sup> strongly suggest that the Wenckebach phenomena (facilitation and inhibition) do not explain this particular type of pacemaker arrhythmia. The examples of this arrhythmia<sup>1</sup> represent the primary and perhaps only situations in which these electrotonic mechanisms have been thought to occur in man. Although there is no a priori reason why the Wenckebach phenomena cannot apply to human cardiac electrophysiology further investigations are needed to document their involvement. Finally, these experiments demonstrate the importance of mechanical events in the pathogenesis of a particular rhythm disturbance. Consideration of the possibility of mechanical factors in arrhythmogenesis may well provide additional examples in the future.

## Summary

The mechanism by which atrial systole influences the efficacy of ventricular capture by a failing pacemaker was investigated in 12 dogs with atrioventricular heart block. Atrial systole caused facilitation of ventricular capture in eight dogs, and inhibition of capture in 10 dogs. Interpolating atrial extrasystoles caused an enhancement or depression of the hemodynamic performance of the atrial systole that affected the efficacy of the pacemaker stimulus. These interpolation experiments showed that atrial systole influenced the efficacy of capture by a mechanical mechanism and not by an electrotonic mechanism. Atrial systole probably caused motion of the endocardial pacing catheter and/or ventricular myocardium. This motion increased or decreased the contact between the pacing electrode and the endocardium with subsequent changes in the efficacy of capture. In three dogs with pacing through epicardial electrodes, atrial systole had no effect on the efficacy of capture.

We would like to thank Dr Eugene Lepeschkin who initially suggested some of these ideas.

## REFERENCES

1. Abernathy W E and Lepeschkin E. The influence of atrial activity on ventricular capture by failing artificial pacemakers. I. Report of two new cases and review of the literature. *AM HEART J* (In press).
2. Spear J F and Moore E N. Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog. *Circ Res* 32:27 1973.
3. Steiner C and Kovalik A T W. A simple technique for production of chronic complete heart block in dogs. *J Appl Physiol* 25:631 1968.
4. Alder H L and Roessler E B. Introduction to probability and statistics. San Francisco 1972. W H Freeman and Company pp 156 175 231.
5. Bigger J T Jr. Electrical properties of cardiac muscle and possible causes of cardiac arrhythmias. In *Cardiac arrhythmias*. Dreifus L S and Likoff W eds. New York 1973. Grune & Stratton Inc p 13.
6. Preston T A. (Letter to editor). Late supernormal excitation. *Am J Cardiol* 38:403 1976.
7. Hoffman B F and Cranefield P F. *Electrophysiology of the heart*. New York 1960. McGraw Hill Book Company Inc chapter 3 p 50.
8. Meyler F L, Nieuwendijk E S and Durrer D. Physiological basis of paired stimulation potentiation. II. Paired pulse stimulation of the heart. Cranefield P F, and Hoffman B F eds. New York 1968. The Rockefeller University Press p 63.
9. Arbel E R, Langendorf R, Pick A and Katz L N. The effect of atrial depolarization on the response to subthreshold stimulation of the ventricle. A preliminary report of clinical and experimental observation. In *Paired pulse stimulation of the heart*. Cranefield P F, and Hoffman B F eds. New York 1968. The Rockefeller University Press p 32.

## Systemic hypertension after surgical treatment of a congenital arteriovenous malformation

Albert P. Rocchini MD  
Amnon Rosenthal MD  
Samuel Schuster MD  
Kenneth E. Fellows Jr MD  
Alexander S. Nadas MD  
Boston, Mass

Systemic hypertension though uncommon in childhood is usually associated with a specific etiology such as renal disease, coarctation of the aorta or pheochromocytoma. We recently encountered severe systemic hypertension resulting from surgical obliteration of a congenital arteriovenous malformation, a heretofore unreported observation in childhood. The purpose of this report is to document this unusual cause for hypertension, suggest a mechanism for its genesis and recommend appropriate therapy.

### Case report

K. S., an 8-year-old Caucasian girl, was noted at birth to have an arteriovenous fistula of the left thigh. Because of hemorrhage following minor trauma, multiple vessels supplying the malformation were ligated at ages 4 and 5. During the subsequent two years, a lump developed as the leg size increased. At age seven, she was admitted to The Children's Hospital Medical Center in Boston. On admission (Oct 2, 1973), a large arteriovenous malformation of the left thigh was present; other findings are outlined in Table 1. A left femoral arteriogram (Fig 1A) demonstrated an extensive arteriovenous malformation of the left leg extending from the inguinal ligament to just below the knee. She was treated with 1,000 rads of radiation (divided over three days) and a one-month course of prednisone (1.5 mg/kg/day). She was readmitted to the hospital on Nov 14, 1973 (Table 1). On Nov 18, 1973, the left hypogastric and profunda femoris arteries and all

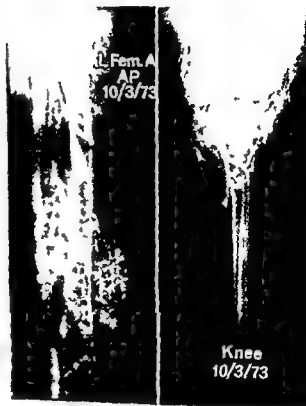


Fig 1 A through C: Arteriograms before (A) two weeks after (B) and eight months after (C) surgical obliteration of a congenital arteriovenous malformation. L. Fem. A = left femoral artery; L. Sup. Fem. = left superficial femoral artery; L. I. A. = left iliac artery; AP = anterior posterior projection.

feeding branches of the left superficial femoral artery were ligated. Her immediate postoperative course was uncomplicated by hypertension (140/110 mm Hg) (Fig 2), a decrease in central venous pressure (70 cm of water to 7 cm of water) and a grand mal seizure. On Nov 19, 1973, a left femoral

From the Departments of Child Radiology and General Surgery, The Children's Hospital Medical Center and the Department of Pediatrics, Harvard Medical School, Boston, Mass.

Supported in part by Training Grant HL05655, Project Grant HL04036 from the National Institutes of Health, Bethesda, Md.

Received for publication Jan 11, 1977.

Accepted for publication Feb 11, 1977.

Reprints Requested: Albert P. Rocchini, MD, Department of Child Radiology, The Children's Hospital Medical Center, 300 Longwood Ave., Boston, MA 02115.

Table I Clinical and laboratory findings

| Date                    | 10/2/73     | 11/14/73 | 11/26/73 | 7/11/74 | 10/31/74    | 7/7/75 |
|-------------------------|-------------|----------|----------|---------|-------------|--------|
| Heart rate (beats/min)  | 156         | 136      | 80       | 100     | 100         | 110    |
| Blood pressure (mm Hg)  | 114/70      | 125/75   | 138/95   | 110/60  | 110/60      | 124/64 |
| Murmurs                 |             |          |          |         |             |        |
| Systolic                | Grade 2/6   | same     | same     | same    | same        | same   |
| Diastolic               | Grade 2/4   | same     | none     | none    | none        | none   |
| Loud S <sub>1</sub>     | yes         | yes      | none     | none    | yes         | yes    |
| Hepatomegaly            | yes         | yes      | none     | none    | none        | none   |
| Chest x ray             | 62          | 63       | 56       | 54      | 56          | 60     |
| (C/T ratio)             |             |          |          |         |             |        |
| Electrocardiogram       | BVH         | BVH      | ~        | normal  | normal      | normal |
| Branham reflex          | Rest        |          |          |         | Rest        |        |
|                         | Compression |          |          |         | Compression |        |
| Heart rate              | 156 100     | —        | —        | —       | 110 72      | —      |
| Blood pressure          | 114/70      | —        | —        | —       | 110/60      | —      |
|                         | 130/95      |          |          |         | 124/98      |        |
| Echocardiogram          |             |          |          |         |             |        |
| Heart rate              | 156 100     | —        | 80       | 100     | 110 75      | —      |
| Stroke volume           | 57 41       | —        | 47       | 69      | 76 58       | —      |
| (ml/beat)               |             |          |          |         |             |        |
| Cardiac index           | 10.4 5.2    | —        | 4.7      | 8.6     | 10.3 5.5    | —      |
| (L/Min/M <sup>2</sup> ) |             |          |          |         |             |        |
| Ejection fraction       | 62 63       | —        | 74       | 62      | 58 60       | —      |

Abbreviations BVH = biventricular hypertrophy C/T Ratio = cardiothoracic ratio

arteriogram demonstrated decreased flow to the arteriovenous malformation above the knee but no significant change distally. On Nov 27 1973 branches of the left popliteal and posterior tibial arteries were ligated. Postoperatively she again developed hypertension (158/115 mm Hg) and a second seizure. A technetium brain scan cerebral angiogram and multiple blood chemistry studies renal function studies 17 ketosteroids and renal arteriogram were all normal. She was initially treated with hydralazine (5 to 7 mg) methyldopa (500 mg/day) and chlorothalidate (600 mg/day) without an effect on the blood pressure. Finally when markedly elevated plasma renin activity was observed (peripheral venous blood 6930 ng per cent/3 hours peripheral venous blood 8171 ng per cent/3 hours left renal vein 10320 ng per cent/3 hours right renal vein 11680 ng per cent/3 hours) (Fig 2 Symbols A, B, C respectively) she was begun on propranolol (initially 10 mg/day then increased to 20 mg/day) with an immediate and marked reduction in both blood pressure and plasma renin activity (1523 ng per cent/3 hours and 1027 ng per cent/3 hours Fig 2 Symbols D and E respectively).

The PRA was assayed in blood taken from an antecubital vein in the recumbent position while on a diet containing between 70 to 90 mg sodium daily. Plasma renin activity assay was by the method of Boucher and associates. Normal values in our laboratory (while on a diet containing 70 to 110 mg sodium daily and obtained in the recumbent position) are up to 1500 ng per cent/3 hours.

Following her second surgery a femoral angiogram (Figure 1B) demonstrated a significant reduction in flow through the arteriovenous malformation. An echocardiogram on Nov 26 1973 demonstrated a marked decrease in cardiac output (Table I). She was discharged from the hospital on propranolol phenobarbital and dilantin. Over the next six months she

remained normotensive and the propranolol was discontinued. On July 9 1974 an arteriogram demonstrated that the arteriovenous malformation had reconstituted itself (Fig 1C). Four months after discontinuation of propranolol (Oct 31 1974) her blood pressure was 110/60 mm Hg however physical examination and echocardiogram suggested the reappearance of high cardiac output (Table I).

She remained well until January 1975 when she developed ulcerations of the skin over the arteriovenous malformation on the anterior aspect of the left thigh. She was hospitalized on Feb 8 1975 after bleeding from the ulcerations at that time her plasma renin activity was 820 ng per cent/3 hours (Fig 2 Symbol F). An arteriogram demonstrated further increase in size of the arteriovenous malformation. Because of a massive sudden hemorrhage her left leg was amputated on Feb 9 1975. Following the amputation she again developed significant systemic hypertension (155/106 mm Hg). Treatment with intermittent doses of intravenous propranolol (0.3 mg) resulted in a rapid return of blood pressure to normal values.

## Discussion

Acute hypertension following temporary occlusion of a large arteriovenous malformation is a well known phenomena (Branham's reflex). The occlusion of the fistula results in an acute increase in peripheral vascular resistance and thereby, blood pressure (Fig 3). However persistent hypertension (seen in our patient) following surgical obliteration of a large arteriovenous malformation although previously reported,<sup>1,2</sup> is



Fig 1B For legend see Fig 1A

poorly understood Holman has proposed that the transient elevation of systolic and diastolic pressure following closure of traumatic arteriovenous fistula is due to distention of the arterial bed by the volume of blood increased in the presence of the fistula. The changes in blood volume following ligation of the fistula observed in patients and experimental animal studies form the basis for this thesis. However in our patient this is not the only explanation since the development of hypertension was also associated with a markedly elevated PRA.

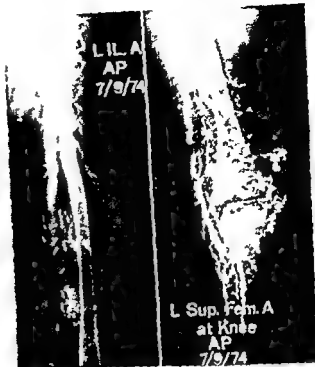


Fig 1C For legend see Fig 1A

The temporal association of increased plasma renin activity with the observed hypertension and the decrease in both plasma renin activity and blood pressure following the administration of propranolol, a possible inhibitor of renin secretion (Fig 2) imply that the increased plasma renin activity may have contributed to the development of systemic hypertension seen in our patient. The other medications, hydralazine and chlorothiazide (all known to affect plasma renin activity) make it difficult to be certain that surgical ligation of the arteriovenous malformation was the only mechanism responsible for the elevation in plasma renin activity. However inspection of Fig 2 shows no clear relationship between any of these drugs and PRA.

The exact mechanism for the rise in plasma renin activity following ligation of an arteriovenous malformation is unknown. The major hemodynamic effects observed were a decrease in central venous pressure (20 to 7 cm of water), a reduction in heart size (cardiothoracic ratio of 63 to 56), a reduction in cardiac output clinically and as determined by echocardiography (cardiac index decreased from 10.4 L/min/M preoperatively to 4.7 L/min/M postoperatively) and a decrease in stroke volume (57 ml/beat preoperatively to 47 ml/beat postoperatively). One might

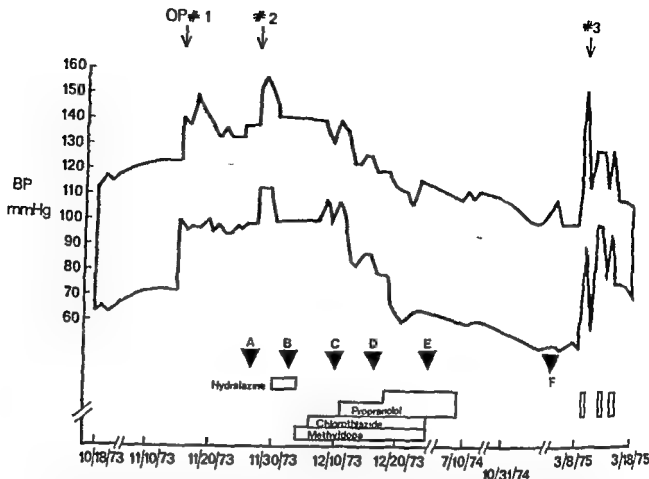


Fig 2 The temporal relationship between surgery, blood pressure, renin level and therapy in the management of a congenital arteriovenous fistula.  $\blacktriangledown$  = plasma renin activity (ng %/3 hr) A = peripheral venous 6930 B = peripheral venous 8171 C = left renal vein 10320 and right renal vein 11660 D = peripheral venous 1523 E = peripheral venous 1027 F = peripheral venous 920 (Maximal normal value for mixed venous plasma renin activity 1500 ng %/3 hr)

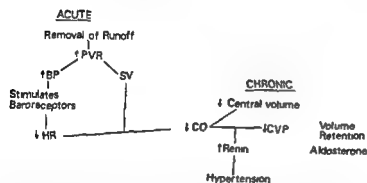


Fig 3 Etiology of hypertension after acute (cuff occlusion) and chronic (ligation) occlusion of a large systemic arteriovenous malformation. In addition to the changes observed after acute removal of the runoff, resection results in hypovolemia increased renin release and sustained hypertension. Abbreviations: PVR = peripheral vascular resistance SV = stroke volume BP = blood pressure HR = heart rate ICVP = central venous pressure CO = cardiac output

speculate that these hemodynamic changes may be responsible for the observed rise in plasma renin activity.

Blood volume is known to be a regulator of plasma renin activity. A number of observations have linked high renin levels with hypovolemia

and volume contracted states.<sup>10</sup> Atrial pressures and volume have also been demonstrated to influence renin secretion in the dog.<sup>11</sup> Since Holman<sup>12</sup> has demonstrated a decrease in plasma volume in five patients following closure of an AVM, and since our patient experienced a decrease in central venous pressure, cardiac output and stroke volume, it seems likely that the central blood volume also decreased in our patient after closure of the arteriovenous malformation. It is therefore possible that having been in a chronic high volume high output state, that the acute decrease in central blood volume after ligation of the arteriovenous malformation was perceived as being abnormal and thereby causing a rise in plasma renin activity. Therefore the rise in plasma renin activity following ligation of the arteriovenous malformation probably represents an attempt to maintain volume homeostasis and the resulting hypertension is a byproduct of these compensatory response (Fig 3).

Regardless of the mechanism, ligation of the

congenital arteriovenous malformation resulted in an increased PRA and in systemic hypertension. The case clearly demonstrates the importance of understanding the genesis of the hypertension so that proper treatment may be administered. Initially the patient was ineffectively treated with hydralazine and chlorothiazide both known to cause some increase in renin secretion.<sup>10</sup> Only after finding that an abnormality in the renin-angiotensin system was responsible for the hypertension was the hypertension effectively controlled with propranolol, an inhibitor of renin secretion.

### Summary

The development of systemic hypertension in an eight year old girl after resection of a large arteriovenous malformation is described. The hypertension was related to an elevated plasma renin activity and was controlled with propranolol. A possible mechanism for the rise in plasma renin activity is postulated.

We wish to thank Dr Clifford Barger for his suggestions and advice in preparing this manuscript.

### REFERENCES

- Loggie J M H. Hypertension in children and adolescents. I. Cause and diagnostic studies. *J Pediatr* 74:331 1969
- Boucher M., Veyrat R., deChamplain J., and Genest J. New procedures for measurement of human plasma angiotensin and renin activity levels. *Can Med Assoc J* 90:194 1964
- Holman, E. Clinical and experimental observation on arteriovenous fistulas. *Ann Surg* 112:840 1940
- Buhler F R, Laragh J H., Baer L., et al. Propranolol inhibition of renin secretion. *N Engl J Med* 287:1209 1972.
- Gavras, H. Brunner H R., and Laragh J H. An angiotensin converting enzyme inhibitor to identify and treat vasoconstriction and volume factors in hypertensive patients. *N Engl J Med* 291:817 1974
- Miller E D Jr, Samuels A L and Haber E. Inhibition of angiotensin conversion and prevention of renal hypertension. *Am J Physiol* 228:448 1975
- Giuseppe M, Romero J C, Shepperd J T. Continuous inhibition of renin release in dogs by vagally innervated receptors in the cardiopulmonary region. *Circ Res* 36:529 1975
- Brennan L A, Malins R L, Jochim K E et al. Influence of right and left atrial receptors on plasma concentration of ADH and renin. *Am J Physiol* 221:273 1971
- Euler M, Julius S and Randall, O. Increased central blood volume in low renin borderline hypertension. *Circulation* 51 and 52 (suppl. II) II:55 1975
- Oparil, A. and Haber E. The renin angiotensin system. *I N Engl J Med* 291:369 1974

### Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. P.O. Box 765, Schenectady, N.Y. 12301 518 374-4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.



# The influence of atrial activity on ventricular capture by failing artificial pacemakers I

## Report of two new cases and review of the literature\*

William S Abernathy, M D  
E Lepeschkin, M D \*\*

Utica N Y and Burlington Vt

Several reports<sup>1-4</sup> have documented cases where the success or failure of ventricular capture by a stimulus from a failing pacemaker depended on the time interval between the stimulus and a preceding P wave. Stimuli falling within a critical P-S interval (the time interval between the beginning of the P wave and the stimulus artifact) exhibited enhanced or diminished efficacy of capture compared to stimuli falling outside this critical interval. This report makes a detailed study of this phenomenon in two new cases and discusses its possible mechanisms.

### Methods

The P-S intervals corresponding to the effective and ineffective stimuli in Cases 1 and 2 were measured with an accuracy of  $\pm 10$  msec from electrocardiograms recorded at 50 mm/sec. The P-S intervals obtained from published electrocardiograms were measured with an accuracy of  $\pm 20$  msec. In some published records it was not possible to identify P waves and consequently not all of the published material was analyzed. Pacemaker stimuli falling within the T wave of a previous ventricular beat were omitted from analysis since the ventricle then would have been in

its refractory period and the stimulus ineffective regardless of its relation to the P wave.

### Case reports

**Case 1** In 1965 a 75 year old man was admitted to the Veterans Administration Hospital Ann Arbor Michigan with angina pectoris, exertional dyspnea, orthopnea and hypertension. Examination showed a blood pressure of 170/88 mm Hg, a II/VI systolic murmur at the apex, a I/VI diastolic murmur at the left sternal margin and a diastolic extra sound. The electrocardiogram revealed complete atrioventricular block and a spontaneous ventricular rhythm at a rate of 40 beats/minute. On roentgenogram the heart size was normal and the mitral annulus was moderately calcified. An asynchronous pacemaker generator (Medtronic Model No. 5870 C code VOO\*) was implanted with a transvenous bipolar pacing catheter (Medtronic Model No. 5816) the tip of which was in the right ventricle. This functioned normally and the man was discharged.

Seven months later the patient was readmitted with a complaint of dizziness when he took a deep breath. The electrocardiograms revealed that the pacemaker stimulus failed to excite the heart during deep inspiration. A chest roentgenogram showed that the tip of the pacing catheter had moved farther away from the apex of the ventricle. The catheter was repositioned with improvement in function but roentgenograms continued to show suboptimal placement of the catheter tip in the right ventricle. One week later the patient again had intermittent pacemaker failure at this time the success or failure of the stimulus bore no relation to respiration or to atrial systole. A short course of prednisolone was given for presumed exit block around the tip of the pacing catheter (see Discussion section). The patient improved and was discharged. One month later intermittent failure of the pacemaker was again documented. Two months later the patient complained of a slow pulse but pacemaker failure was not documented.

One year later (23 months after initial implantation) electrocardiograms recorded over a period of 42 days revealed intermittent failure of the pacemaker stimulus to excite the heart. These electrocardiograms form the basis of this report.

From the Masonic Medical Research Laboratory, Utica N Y and the Department of Medicine, University of Vermont, Burlington Vt.  
Received for publication Sept. 13, 1977.  
Accepted for publication Oct. 31, 1977.

Reprint Requests: William S. Abernathy, M.D., Masonic Medical Research Laboratory, Utica N.Y. 13501.

This work was begun while both authors were at the Heart Station, University Hospital, Ann Arbor, Mich.

Supported by Research Career Award 5 K6 HL 440 from the National Institute of Health, U.S. Public Health Service.

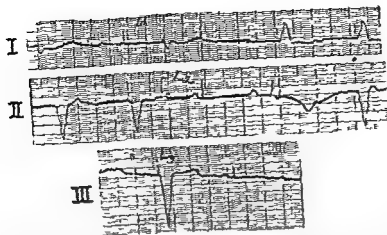


Fig 1 Case 1 Electrocardiographic Leads I (recorded Feb 12 1967) II and III (recorded Mar 24 1967) The dots above the strips indicate the positions of the pacemaker artifacts. Recorded at 50 mm/sec., one large horizontal division = 200 msec., two large vertical divisions = 1 mV

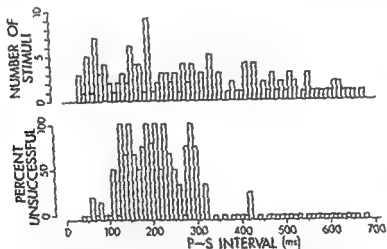


Fig 2 Case 1 Top Number of stimuli that occurred at each P-S interval (time interval in msec between the stimulus artifact and the onset of the preceding P wave) Bottom Percent of pacemaker stimuli that were unsuccessful in ventricular capture at each P-S interval.

and am presented below. Chest roentgenograms were unchanged. Prednisolone and ephedrine were given for presumed embolus but were not effective (see Discussion section). Subsequently the old pacemaker system was removed, new pacemaker leads were sutured to the left ventricular epicardium and a new generator was implanted. Testing of the explanted generator by the manufacturer showed a 500 per cent depletion of cell No. 1 with a total generator output of 4.1 volts compared to 5.0 volts originally. The new pacemaker system functioned normally for the next 5 years, at which time the patient died of uremia. At autopsy the heart weighed 450 grams, there was moderate atherosclerosis of the coronary arteries and the mitral valve was calcified and stenotic.

**Case 2** In 1933 a 73-year-old woman was admitted to University Hospital, Ann Arbor, Michigan with angina pectoris and nocturnal and exertional dyspnea. Examination

revealed a blood pressure of 195/84 mm Hg, moderately severe kyphoscoliosis and pectus excavatum, a previous left mastectomy, a II/VI systolic murmur at the left sternal margin and third and fourth heart sounds. The electrocardiogram was normal except for 2:1 atrioventricular block. A moderately enlarged heart and the thoracic deformities noted above were present on the roentgenogram. A unipolar demand generator (Medtronic Model No. 343, code VVI 1) and transvenous pacing catheter (Medtronic Model No. 6909) the tip of which was in the right ventricle were installed. Initially the pacemaker functioned normally but nine days after implantation the pacemaker stimulus intermittently failed to excite the heart. The electrocardiograms documenting this failure registered for four days form the basis of this report and are presented below. A repeat roentgenogram of the chest, when compared with one taken a week earlier showed a new upward displacement of the tip of the pacing

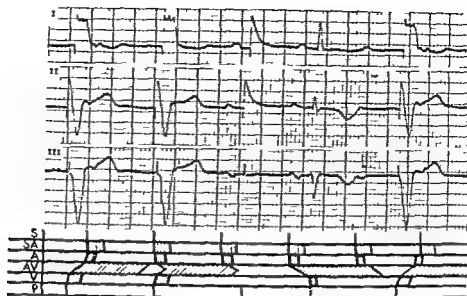


Fig 3 Case 2 Non simultaneous electrocardiographic Leads I II and III The diagram at the bottom is a proposed analysis of Lead III Recorded at 50 mm/sec one large horizontal division = 200 msec two large vertical divisions = 1 mV Abbreviations A = atrium AV = atrioventricular junction P = pacemaker S = sinus node SA = sinoatrial junction V = ventricle The stippled areas (in A and V) indicate the P waves and the QRS complexes The striped areas (in SA and AV) indicate the refractory periods of those tissues

catheter The tip continued to be located near the apex of the right ventricle The catheter was repositioned with subsequently normal pacing function for the next three years (up to the time last seen)

## Results and review

The electrocardiographic data for Case 1 are presented in Figs 1 and 2 In Fig 1 the P waves appear at a faster rate than the pacemaker stimuli In Lead I the first two beats are ventricular escape beats and the last two beats are paced The first and third pacemaker discharges (artifacts) do not capture the ventricle because they fall in the refractory periods of the escape beats The second pacemaker discharge appears outside of the refractory period but does not capture the ventricle it is preceded by a P wave with a P S interval of 275 msec In Lead II, the first second and fourth beats are paced the third beat is an escape beat A P wave precedes the third pacemaker discharge by 155 msec and this discharge does not excite the ventricle The fourth artifact falls in the refractory period of the escape beat In Lead III the single beat present is paced, the second pacemaker stimulus does not excite the ventricle (P S interval = 140 msec) In this figure note the variation in P S intervals associated with inhibition of ventricular capture by atrial activity note that the electrocardiogram shows only Ta waves but no ventricular activity after the stimuli preceded by P waves (second stimuli in Leads I and III third stimulus

in Lead II), and note that there are no conducted beats present

Fig 2 summarizes all of the electrocardiographic data, 139 stimuli are analyzed For P S intervals between 110 and 320 msec 68 per cent of the stimuli were unsuccessful in excitation For P S intervals less than 110 msec or greater than 320 msec 4 per cent of the stimuli were unsuccessful This difference is statistically significant (Chi squared with Yates correction = 60.9  $p < 0.001$ )

Case 2 is illustrated in Figs 3 to 5 In Fig 3 the first complex in each lead consists of a unipolar pacemaker artifact followed by and superimposed upon a wide QRS which in turn is followed by a biphasic P wave As indicated in the analysis of Lead III at the bottom of the figure the first complex is a paced beat with retrograde atrial activation The second complex is similar to the first except that it shows no separate P wave instead a non conducted sinus P wave is superimposed on the paced QRS complex The third complex consists of a sinus P wave followed 170 to 200 msec later by a pure pacemaker artifact This artifact has an initial slender upward deflection followed by a broad terminal portion corresponding to the decay of the electrode polarization Since the generator was located in the right infraclavicular fossa the vector of the pacemaker artifact is nearly perpendicular to Lead III where the size of the artifact is minimal Since both the

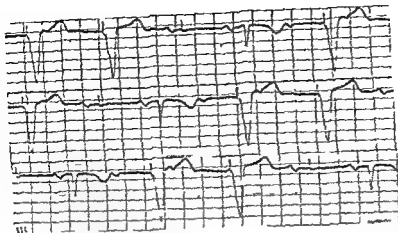
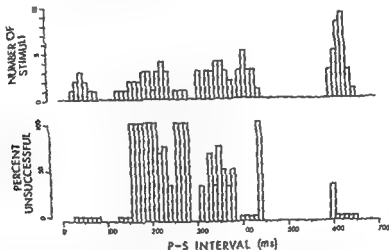


Fig 4 Case 1 Continuous electrocardiographic Lead III Recorded at 50 mm/sec one large horizontal division = 200 msec two large vertical divisions = 1 mV



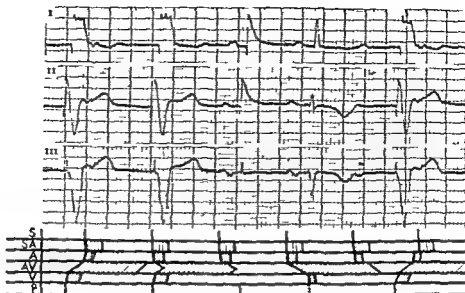


Fig 3 Case 2 Non simultaneous electrocardiographic Leads I II and III The diagram at the bottom is a proposed analysis of Lead III Recorded at 50 mm/sec one large horizontal division = 200 msec two large vertical divisions = 1 mV Abbreviations A = atrium AV = atrioventricular junction P = pacemaker S = sinus node SA = sinoatrial junction V = ventricle The stippled areas (in A and V) indicate the P waves and the QRS complexes The striped areas (in SA and AV) indicate the refractory periods of those tissues

catheter The tip continued to be located near the apex of the right ventricle The catheter was repositioned with subsequently normal pacing function for the next three years (up to the time last seen)

### Results and review

The electrocardiographic data for Case 1 are presented in Figs 1 and 2 In Fig 1 the P waves appear at a faster rate than the pacemaker stimuli In Lead I the first two beats are ventricular escape beats and the last two beats are paced The first and third pacemaker discharges (artifacts) do not capture the ventricle because they fall in the refractory periods of the escape beats The second pacemaker discharge appears outside of the refractory period but does not capture the ventricle it is preceded by a P wave with a P S interval of 275 msec In Lead II the first second, and fourth beats are paced the third beat is an escape beat A P wave precedes the third pacemaker discharge by 155 msec and this discharge does not excite the ventricle The fourth artifact falls in the refractory period of the escape beat In Lead III the single beat present is paced, the second pacemaker stimulus does not excite the ventricle (P S interval = 140 msec) In this figure note the variation in P S intervals associated with inhibition of ventricular capture by atrial activity note that the electrocardiogram shows only Ta waves but no ventricular activity after the stimuli preceded by P waves (second stimuli in Leads I and III, third stimulus

in Lead II), and note that there are no conducted beats present

Fig 2 summarizes all of the electrocardiographic data 139 stimuli are analyzed For P S intervals between 110 and 320 msec 68 per cent of the stimuli were unsuccessful in excitation For P S intervals less than 110 msec or greater than 320 msec 4 per cent of the stimuli were unsuccessful This difference is statistically significant (Chi squared with Yates correction = 609  $p < 0.001$ )

Case 2 is illustrated in Figs 3 to 5 In Fig 3 the first complex in each lead consists of a unipolar pacemaker artifact followed by and superimposed upon a wide QRS which in turn is followed by a biphasic P wave As indicated in the analysis of Lead III at the bottom of the figure the first complex is a paced beat with retrograde atrial activation The second complex is similar to the first except that it shows no separate P wave instead a non conducted sinus P wave is superimposed on the paced QRS complex The third complex consists of a sinus P wave followed 170 to 200 msec later by a pure pacemaker artifact This artifact has an initial slender upward deflection followed by a broad terminal portion corresponding to the decay of the electrode polarization Since the generator was located in the right infraclavicular fossa the vector of the pacemaker artifact is nearly perpendicular to Lead III where the size of the artifact is minimal Since both the

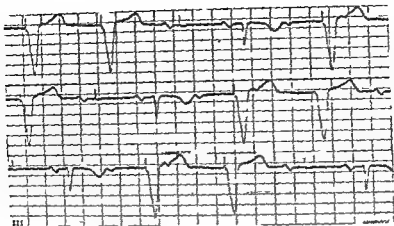


Fig 4 Case 2 Continuous electrocardiographic Lead III Recorded at 50 mm/sec (one large horizontal division = 50 msec two large vertical divisions = 1 mV)

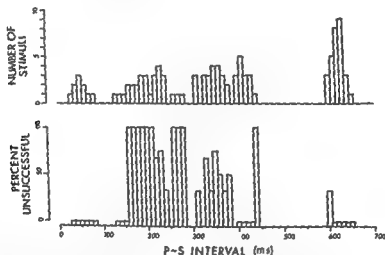


Fig 5 Case 2 Top Number of stimuli occurring at each P S interval (defined as in Fig 2) Bottom Per cent of pacemaker stimuli that were unsuccessful in ventricular capture for each P S interval

paced beats (first second and fifth complexes) and the conducted beats (fourth complexes) show a large negative QRS in Lead III a fusion beat also would have had a large negative QRS in Lead III. However the negative deflection following the third stimulus is too small to have been part of a fusion beat. Hence it is apparent that this stimulus was inhibited by the preceding atrial activity and that there was no ventricular activation following the third stimulus. The fourth complex is a conducted beat with a P R interval of 190 msec. Atrioventricular conduction occurred at this point because as indicated in the diagram the preceding pacemaker stimulus was ineffective because the preceding P wave was blocked and because the underlying rhythm before pacing was 2:1 atrioventricular block. The

conducted beat inhibited the pacemaker generator as indicated by the broken line in the diagram. The last complex is similar to the first one.

Fig 4 shows a longer example of the repeating pattern intermittently present in this patient. Two paced beats are followed by an unsuccessful stimulus and then by a conducted beat. This pattern results from the relative atrial and ventricular rates, the demand nature of the pacemaker, the 2:1 atrioventricular block, and the influence of atrial activity on the pacemaker.

Fig 5 presents the analysis of 105 stimuli for P S intervals between 160 and 380 msec. 69 per cent of the stimuli were unsuccessful in excitation. For P S intervals outside this range 4 per cent of the stimuli were unsuccessful. This differ-

Table 1 Synopsis of published cases demonstrating the influence of atrial activity on failing pacemakers

| Author & reference                                      | Range of critical P S intervals (msec) | Number of stimuli showing the influence† | Type of heart block | Type of catheter | Proposed mechanism |
|---|--|--|---------------------|------------------|--------------------|
| Cases in which atrial activity inhibited the stimulus   |  |  |                     |                  |                    |
| Dreifus Fig 11 9  | 170 300                                | 7  | —                   | —                | —                  |
| Sanz  | 280 320                                | 301                                      | A AVB‡              | Endo             | WI                 |
| Preston   | 100 400                                | —  | A AVB               | Endo             | ME                 |
| Danzig  | 80-100                                 | 14                                       | A AVB               | Endo             | WI                 |
| Abernathy Case 1 (This report)                          | 110 320                                | 42                                       | A AVB               | Endo             | ME                 |
| Abernathy Case 2 (This report)                          | 160 380                                | 33                                       | 2:1 AVB             | Endo             | ME                 |
| Cases in which atrial activity facilitated the stimulus |  |  |                     |                  |                    |
| Soloff Fig 3  | 50 180                                 | 8  | None                | Epi              | —                  |
| Igarashi Case 2   | 140                                    | 1  | AVB                 | Endo             | WF                 |
| Igarashi Case 8   | —                                      | —  | —                   | Endo             | WF                 |
| Igarashi Case 10 Fig 6B                                 | 160                                    | 1  | None                | Endo             | WF                 |
| Arbel Human Case  | 40 440                                 | 7  | A AVB               | Endo             | WF                 |
| Arbel Canine Case                                       | 10 80                                  | 7  | None                | Epi              | WF                 |
| Dreifus Fig 11 11                                       | 90 200                                 | 3  | A AVB               | —                | WF                 |
| Kisch   | 60 110                                 | 4  | 2:1 AVB             | —                | WF                 |
| Dreifus Fig 11 12                                       | 100 140                                | 4  | —                   | —                | WF                 |
| Castellanos Fig 11 (Tracing on Fig 12)                  | 90 100                                 | 2  | None                | —                | WF                 |

The P S intervals during which atrial activity exerted its influence on the efficacy of ventricular capture

†The number published in the text of the article or the number obtained by counting from the published electrocardiograms.

‡Symbols and abbreviations: A AVB = advanced atrioventricular block; AVB = atrioventricular block; Endo = endocardial (transvenous) pacing catheter; Epi = epicardial (myocardial) pacing catheter; ME = mechanical effects; P S interval = time interval in msec from the stimulus to onset of preceding P wave; WF = Wenckebach facilitation; WI = Wenckebach inhibition. The symbol (—) means that the datum was not available in the published report.

ence is statistically significant (Chi squared with Yates correction = 47.0  $p < 0.001$ ).

A search of the literature yielded 24 additional cases in which atrial activity influenced the efficacy of a failing pacemaker. These cases are listed in Table 1. There are 14 cases in which atrial activity decreased the efficacy of the pacemaker. Data obtained from measurements of published electrocardiograms of one of these cases are presented in Fig 6; no clinical details are available. For P S intervals between 170 and 300 msec 87 per cent of the stimuli were unsuccessful outside this range of P S intervals none of the stimuli were unsuccessful. This difference is statistically significant (Chi squared with Yates correction = 10.9  $p < 0.001$ ). The case reported by Sanz and colleagues showed a similar range of critical P S intervals (Table 1). In this case there was a fractured endocardial pacing catheter with an abnormally high threshold. The inhibition of pacing by atrial activity was present for 5 hours. Preston<sup>1</sup> published an abstract describing 11 cases in which the pacing voltage was deliberately set just at the threshold for pacing the P S intervals

during which the inhibition occurred were approximately 100 to 400 msec (Preston personal communication). The final case in this group was reported by Danzig and Diamond.<sup>4</sup> In this case the critical P S intervals were shorter (80 to 100 msec) than in the other cases described above. Of 17 stimuli with P S intervals of 80 to 100 msec three were successful in excitation; eight were unsuccessful and six were successful but had a QRS with an unusual appearance. Stimuli occurring at other P S intervals were successful. In Danzig and Diamond's case the inhibition disappeared when the current supplied by the generator was increased.

Facilitation of capture by the pacemaker stimulus was observed in nine human and one canine cases (Table 1). In this group only Soloff and Fewell<sup>5</sup> described detailed clinical data. Their patient had an epicardial pacing catheter which had migrated away from the site of initial implantation. In the three cases studied by Igarashi and Ayabe<sup>6</sup> the pacemaker current was intentionally set to various low levels before the data were collected. In the other five human cases the

clinical data are insufficient to determine if there was malfunction of the pacemaker. In the canine experiment of Arbel and co workers' the current supplied by the pacemaker was set below the level necessary for completely successful pacing.

Inspection of Table I reveals that the critical P-S intervals tended to be shorter in those cases where atrial activity facilitated the stimulus as compared to those cases where atrial activity inhibited the stimulus. With the exception of the cases of Arbel and colleagues' facilitation occurred with P-S intervals of 50 to 200 msec and inhibition was associated with P-S intervals of 80 to 400 msec. In Arbel and colleagues' human case although atrial activity favorably influenced ventricular capture during P-S intervals of 40 to 440 msec the peak effect was with P-S intervals of 100 to 200 msec. Arbel and associates' canine case is probably not directly comparable to the human cases since the heart rate was relatively fast (160 beats/minute).

In two cases interpreted as facilitation none of the pacemaker stimuli actually failed to excite the heart. In one case (1 Fig 11 12) the QRS of the paced beats had an unusual appearance when the stimulus fell within a critical P-S interval. In the other case ventricular premature beats occurred only following fusion beats (sinus and paced) arising from a critical P-S interval.

The type of pacing catheter was reported in 21 of the 26 cases. In 19 of the 21 cases there was an endocardial catheter. Of the two epicardial catheters one was the malfunctioning catheter described by Soloff and Fewell<sup>3</sup> and the other was used in the canine experiment of Arbel and colleagues.

## Discussion

The observations presented above indicate that a suitably timed atrial beat can influence a failing pacemaker by facilitating stimuli which are usually unsuccessful in exciting the heart by inhibiting stimuli which are generally successful or by changing the appearance of the QRS of paced beats. This influence is exerted by atrial activity which precedes a stimulus by a critical time interval and the values of that interval are uniquely defined for each case. The critical P-S intervals are shorter (usually 40 to 200 msec) in cases of facilitation than in cases of inhibition (80 to 400 msec) but there is considerable overlap.

**Pacemaker failure.** Both of our cases demon-

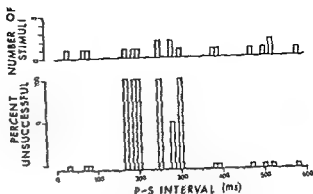


Fig 6 Data for this figure were obtained from a previously published electrocardiogram. Top: Number of stimuli occurring at each P-S interval (defined as in Fig 2). Bottom: Percent of stimuli that were unsuccessful in ventricular capture for each P-S interval.

strated overt failure of the pacemaker system (generator and/or catheter). In Case 1 the generator had a depleted cell. Whether or not a suboptimally positioned catheter also contributed to the failure is uncertain. Proper therapy in Case 1 was replacement of the pacemaker, not administration of prednisolone and ephedrine. In Case 2 the pacing catheter was malpositioned and repositioning the catheter corrected the problem.

When the available data from the previously reported cases are examined, it is evident that all of the pacemaker systems were failing at the time atrial activity exerted its influence on the efficacy of capture. The presence of this phenomenon is an indication for appropriate diagnostic and therapeutic measures to correct the pacemaker failure.

**Electrotonic mechanism.** Electrotonic and mechanical mechanisms have been proposed as alternative explanations for the influence of atrial activity. Table I indicates the explanations preferred in previous articles. A discussion of these mechanisms follows.

**Wedensky facilitation** (as distinguished from the Wedensky effect) is said to occur when an effective stimulus originating above a site of conduction block renders a subthreshold stimulus below the site of block successful in excitation.<sup>1,2</sup> Excitation of the normally conducting cells proximal to the block gives rise to a current which spreads passively through the cells distal to the block (electrotonic current). Facilitation is thought to occur because electrotonic current



from the blocked impulse combines additively with local current from the subthreshold stimulus. Facilitation and summation have been demonstrated by microelectrode studies in canine Purkinje fibers.<sup>14, 15</sup> Wedensky inhibition is said to occur when an effective stimulus, originating above the site of conduction block, causes a supra-threshold stimulus below the block to fail in excitation. Cranefield and Hoffman<sup>14</sup> have observed that impulses in depressed canine Purkinje fibers can be inhibited by previous stimulation of other anastomosing fibers. They have suggested<sup>14</sup> that, although the basis of Wedensky inhibition remains unclear, these observations may be the mechanism of Wedensky inhibition.

An electrotonic mechanism (Wedensky facilitation or inhibition) has been favored by nearly all previous authors as the explanation for the influence of atrial activity on ventricular capture by failing pacemakers (Table I). This mechanism requires that current derived from atrial excitation (the P wave) traverse an area of conduction block and exert an electrotonic effect near the tip of the pacing catheter. Electrotonic spread can be expected to extend for at most a few millimeters beyond the site of block because the space constant of the conducting tissue is short.<sup>16</sup> Thus there are only two conditions under which the Wedensky phenomena could have operated in these cases. First if the pacemaker stimulus gave rise to a fusion beat this would naturally imply that the atrial excitation was conducted through the atrioventricular junction and excited the ventricles. The excited ventricular tissue could have electrotonically influenced the pacemaker stimulus. There are five cases<sup>1</sup> (Fig. 11, 12, 13, 14, 15) where at least some of the time atrial systole exerted its influence in the presence of a fusion beat.

Second, if the atrioventricular block were caused by bilateral peripheral bundle branch block atrial excitation could propagate to the terminal bundle branches. An electrotonic current originating at this point could then influence the efficacy of the pacemaker. There are 2 cases with wide ( $> 120$  msec) unpaced QRS complexes and atrioventricular block.<sup>2, 3, 16, 17</sup> An electrotonic mechanism could have operated in these cases if there was bilateral peripheral bundle branch block.

However, if the site of the block were in the atrioventricular node or His bundle the distance between the site of block and the pacing electrode

would be too great for an electrotonic spread to influence the stimulus. Both of our cases had atrioventricular block and narrow ( $< 120$  msec) QRS complexes in the absence of pacing. In Case 1 these were escape beats and in Case 2 these were conducted beats. There are an additional three cases with narrow unpaced QRS complexes, atrioventricular block, and no fusion beats<sup>1</sup> (Fig. 11, 13, 14, 15, 16, 17, 18, 19, 20). That the QRS was narrow favors the site of block being in the atrioventricular junction.<sup>18</sup> Hence, in these five cases it is difficult to accept the Wedensky phenomena as being the explanation for the influence of atrial activity.

In summary, of the 12 cases for which there are adequate electrocardiographic data, the Wedensky phenomena theoretically could have operated in seven and probably could not have operated in five. (There are 14 cases<sup>1</sup> (Fig. 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) for which information on either the QRS duration or the atrioventricular conduction was not given.)

**Mechanical mechanism.** An alternative explanation is that atrial systole causes motion of the pacing catheter and/or ventricular myocardium and that this motion alters the efficacy of ventricular capture by increasing or decreasing the contact between the catheter electrode and the ventricle. Several previous authors<sup>4, 5, 19, 20</sup> have noted this possibility, but few have favored it (Table I).

Table II lists some electromechanical and mechanical intervals which are relevant to this discussion. (We are unaware of more complete data on the motion of the right atrium and ventricle.) Right atrial motion may begin as soon as 58 msec after the onset of the P wave. If the right atrial contraction were similar to the left atrial contraction the right atrial contraction wave could last over 100 msec (Table II). In terms of the atrial contribution to ventricular motion, experimental studies<sup>1, 21</sup> indicate that a suitably timed atrial systole improves ventricular function in part by augmenting ventricular diastolic volume. Several studies<sup>22, 23</sup> in man have shown that atrial systole favorably affects ventricular performance when the P-R interval ranges between 100 and 400 msec and that the maximum effect occurs with P-R intervals of approximately 150 to 300 msec. Moreover studies with the apexcardiogram in man (Table II) have demonstrated that atrial systole causes diastolic ventricular motion which may begin as soon as 50

msec after the P wave and which may continue for over 300 msec after the onset of the P wave

These observations suggest two ways in which atrial systole may influence a pacemaker stimulus. First atrial contraction may move the pacing catheter if part of the catheter is in intimate contact with the atrial wall. This movement could push the catheter closer to the ventricular wall thus enhancing the efficacy of capture. However in the presence of a broken catheter lead this motion could separate the broken ends through twisting or bending of the catheter apparent inhibition of the pacemaker stimulus would result. Second atrial systole could move the ventricular wall relative to the catheter. This movement would be caused by an expanding ventricular diastolic volume and would occur 100 to 400 msec after the onset of the P wave. This ventricular motion could increase or decrease the contact between the pacing electrode and the endocardium with subsequent changes in the efficacy of capture.

Sanz and associates rejected a mechanical mechanism because they thought that the effects of atrial systole would not last more than 200 msec after the onset of the P wave. In our opinion this objection is invalid since our review has shown that atrial systole can influence ventricular motion up to 400 msec after the P wave. Igarashi and Ajabe<sup>11</sup> state that the observation of facilitation with epicardial electrodes is incompatible with a mechanical mechanism. For reasons outlined in another report<sup>12</sup> we do not agree with this objection.

Because right atrial and ventricular hemodynamics have not been investigated as fully as those on the left side we are unable to state conclusively that in man atrial systole can mechanically influence a pacing catheter as described above. However we think the probability is high that right atrial systole exerts mechanical effects sufficient to explain most if not all of the cases under consideration. This supposition is strengthened by the report of Preston<sup>13</sup> who radiographically observed movement of the pacing catheter related to atrial systole in eight patients. Moreover recent experimental work provides additional support for the mechanical explanation. The mechanical mechanism has the advantages of being relatively simple conceptually of being a single mechanism for the diverse changes in pacing function related

Table II Electromechanical and mechanical intervals involving atrial systole

| Interval   | Time (msec) | Reference |
|--|-------------|-----------|
| Onset of P wave to onset of right atrial systole | 58-72       | 34        |
| Onset of P wave to onset of left atrial systole  | 76-94       | 34        |
| Onset to peak of left atrial contraction wave    |             |           |
| Normal subjects                                  | 30-80       | 35        |
| average  | 55          |           |
| Diseased subjects                                | 50-140      | 35        |
| average  | 87          |           |
| Onset of P wave to A wave of apexcardiogram      | 120-140     | 36        |
| average  | 140         |           |
| 80-160   |             | 37        |
| average  | 110         |           |
| 80-120   |             | 38        |
| Duration of A wave of apexcardiogram             |             |           |
| Normal subjects                                  | 20-50       | 38        |
| 30-130   |             | 39        |
| average  | 60          |           |
| Diseased subjects                                | 40-260      | 39        |
| average  | 90          |           |

to atrial systole and of being independent of the presence or site of atrioventricular block

### Summary

Atrial activity can influence the ability of a failing artificial pacemaker to excite the heart. An appropriately timed atrial beat may cause failure in excitation by pacemaker stimuli which are usually successful in ventricular capture. Conversely stimuli which usually fail in excitation may be made to succeed by an appropriately timed atrial beat. Two case reports and a review of the literature are presented. Alternative mechanisms for this influence of atrial activity are electrotonic effects (Wedensky facilitation or inhibition) and mechanical effects (motion of the pacing catheter or ventricular myocardium). The authors consider the latter mechanism preferable.

We wish to thank Dr. Thomas A. Preston who provided the material for Case 1 and Dr. Arthur B. Simon who gave us permission to use the material for Case 2.

### Addendum

After this manuscript was prepared an article appeared with additional examples of the influence of atrial systole on pacemaker capture (Goldberg E. Mechanical factors and the elec

from the blocked impulse combines additively with local current from the subthreshold stimulus. Facilitation and summation have been demonstrated by microelectrode studies in canine Purkinje fibers.<sup>14,16</sup> Wedensky inhibition is said to occur when an effective stimulus originating above a site of conduction block, causes a supra-threshold stimulus below the block to fail in excitation. Cranefield and Hoffman<sup>14</sup> have observed that impulses in depressed canine Purkinje fibers can be inhibited by previous stimulation of other anastomosing fibers. They have suggested<sup>17</sup> that, although the basis of Wedensky inhibition remains unclear, these observations may be the mechanism of Wedensky inhibition.

An electrotonic mechanism (Wedensky facilitation or inhibition) has been favored by nearly all previous authors as the explanation for the influence of atrial activity on ventricular capture by failing pacemakers (Table I). This mechanism requires that current derived from atrial excitation (the P wave) traverse an area of conduction block and exert an electrotonic effect near the tip of the pacing catheter. Electrotonic spread can be expected to extend for at most a few millimeters beyond the site of block because the space constant of the conducting tissue is short.<sup>18</sup> Thus, there are only two conditions under which the Wedensky phenomena could have operated in these cases. First, if the pacemaker stimulus gave rise to a fusion beat, this would naturally imply that the atrial excitation was conducted through the atrioventricular junction and excited the ventricles. The excited ventricular tissue could have electrotonically influenced the pacemaker stimulus. There are five cases<sup>1, 6, 10, 11, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</sup> where at least some of the time atrial systole exerted its influence in the presence of a fusion beat.

Second, if the atrioventricular block were caused by bilateral peripheral bundle branch block, atrial excitation could propagate to the terminal bundle branches. An electrotonic current originating at this point could then influence the efficacy of the pacemaker. There are 2 cases with wide (> 120 msec) unpaced QRS complexes and atrioventricular block.<sup>24, 100, 101</sup> An electrotonic mechanism could have operated in these cases if there was bilateral peripheral bundle branch block.

However, if the site of the block were in the atrioventricular node or His bundle, the distance between the site of block and the pacing electrode

would be too great for an electrotonic spread to influence the stimulus. Both of our cases had atrioventricular block and narrow (< 120 msec) QRS complexes in the absence of pacing. In Case 1 these were escape beats, and in Case 2 these were conducted beats. There are an additional three cases with narrow unpaced QRS complexes, atrioventricular block, and no fusion beats.<sup>1 (Fig. 11), 4, 7, 10, 11</sup> That the QRS was narrow favors the site of block being in the atrioventricular junction.<sup>10</sup> Hence in these five cases it is difficult to accept the Wedensky phenomena as being the explanation for the influence of atrial activity.

In summary, of the 12 cases for which there are adequate electrocardiographic data, the Wedensky phenomena theoretically could have operated in seven and probably could not have operated in five. (There are 14 cases<sup>1 (Fig. 11), 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</sup> for which information on either the QRS duration or the atrioventricular conduction was not given.)

**Mechanical mechanism.** An alternative explanation is that atrial systole causes motion of the pacing catheter and/or ventricular myocardium and that this motion alters the efficacy of ventricular capture by increasing or decreasing the contact between the catheter electrode and the ventricle. Several previous authors<sup>1, 2, 3, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</sup> have noted this possibility, but few have favored it (Table I).

Table II lists some electromechanical and mechanical intervals which are relevant to this discussion. (We are unaware of more complete data on the motion of the right atrium and ventricle.) Right atrial motion may begin as soon as 58 msec after the onset of the P wave. If the right atrial contraction were similar to the left atrial contraction, the right atrial contraction wave could last over 100 msec (Table II). In terms of the atrial contribution to ventricular motion, experimental studies<sup>11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</sup> indicate that a suitably timed atrial systole improves ventricular function in part by augmenting ventricular diastolic volume. Several studies<sup>23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</sup> in man have shown that atrial systole favorably affects ventricular performance when the P-R interval ranges between 100 and 400 msec and that the maximum effect occurs with P-R intervals of approximately 150 to 300 msec. Moreover, studies with the apexcardiogram in man (Table II) have demonstrated that atrial systole causes diastolic ventricular motion which may begin as soon as 80

# Clinical pathologic conference

## A discussion on hypertrophic cardiomyopathy

Thomas L. Spray, MD  
Barry J. Maron, MD  
Andrew G. Morrow, MD  
Stephen F. Epstein, MD  
William C. Roberts, MD  
Bethesda, Md

**DR. ROBERTS** The purpose of this conference is to discuss certain clinical, operative, and morphologic features of hypertrophic cardiomyopathy as exemplified in one patient. Dr. Spray will present the patient.

**DR. SPRAY** R. H. (11-65-60-4), a 56-year-old white woman, was not suspected of having heart disease until she was 30 years old, when a precordial murmur was heard. She was in good health until age 40, when she developed angina pectoris and palpitations. From age 51 on, her symptoms increased in frequency and severity. In addition, she developed orthopnea and paroxysmal nocturnal dyspnea. During the year before death, occasional syncopal and presyncopal episodes occurred. In February 1976, she was admitted to a local hospital where an electrocardiogram showed left ventricular hypertrophy with the strain pattern. A treadmill exercise tolerance test was attempted but it was stopped when she developed paroxysmal atrial tachycardia. Cardiac catheterization disclosed the following pressures (in mm Hg): right ventricle (body) 50/3; right ventricle (subpulmonic area) 21/3; pulmonary trunk 21/17 (mean 12); pulmonary arterial wedge mean 7; left ventricle (body) 235/0-25; left ventricle (subaortic area) 105/12; and aorta 105/60 (mean 80). The peak systolic pressure gradient between left ventricle and aorta was 130 mm Hg. The cardiac output was 4.7 liters per minute and the cardiac index 3.0 liters/minute/M<sup>2</sup>. She was

begun on propranolol (160 mg per day) and quinidine.

In May 1976, she was admitted to a local hospital for treatment of severe headache at which time diastolic blood pressures to 130 mm Hg were noted. Diazoxide therapy resulted in marked hypotension which required intravenous metaraminol for stabilization. She was admitted to the National Heart, Lung, and Blood Institute 19 days before death.

On examination, the blood pressure was 120/80 mm Hg, heart rate 56 per minute, and respiratory rate 12 per minute. The jugular venous pulse was normal. The carotid arterial upstroke was judged to be rapid. The lung fields were clear to auscultation. The point of maximal cardiac impulse was in the sixth left intercostal space in the anterior axillary line and the apical beat had a triple character. The first and second heart sounds were normal; a fourth heart sound was present at the apex. A Grade 4/6 systolic ejection type murmur was heard loudest at the apex and it radiated to the base. The murmur increased in intensity on standing but did not change with Valsalva maneuver. Neither liver nor spleen were palpated but mild pedal edema was noted.

**DR. ROBERTS** Dr. Maron, could you describe the electrocardiogram, chest roentgenogram, and echocardiogram?

**DR. MARON** The electrocardiogram shows left ventricular hypertrophy with strain pattern (Fig. 1). In addition, the T waves in Leads I and aV<sub>1</sub> are deeply inverted in a symmetric fashion. ST segments are elevated in Leads V<sub>1</sub> and V<sub>2</sub> and depressed in Leads V<sub>3</sub> and V<sub>4</sub>. Left atrial enlargement also is evident. The chest radiograph shows pectus excavatum, left ventricular enlargement,

From the Pathology, Cardiology, and Surgery Branches, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.

Received for publication May 3, 1977.

Reprint requests: William C. Roberts, MD, Bldg. 10A, Room 3E-30 NIH, Bethesda, Md. 20814.

trocadiogram, AM HEART J 93 629, 1977) Figs 5 through 8 in that article illustrate several clinical cases. In one case, fluoroscopy confirmed movement of the pacing catheter induced by atrial systole.

## REFERENCES

- Dreifus L S Chapter 11 in *Current concepts of cardiac pacing and cardioversion* Meltzer L E and Kitchell J R eds Philadelphia 1971 The Charles Press p 217
- Sanz G Van Loon G R and Schwartz L Phasic pacemaker failure J Electrocardiol 8 267 1973
- Preston T A Atrial phasic inhibition of implanted cardiac pacemakers (Abstract) Circulation 37 and 38 (Suppl VI) 168 1968
- Danzig R and Diamond G Increase in threshold to ventricular activation related to atrial contraction A possible example of Wenckebach inhibition AM HEART J 82 531 1971
- Soloff L A and Fewell J W The supernormal phase of ventricular excitation in man Its bearing on the genesis of ventricular premature systoles and a note on atrioventricular conduction AM HEART J 59 869 1960
- Igarashi M, and Ayabe T Quantitative study of the supernormal phase of ventricular excitability in man Am J Cardiol 36 292 1975
- Arbel E R Langendorf R Pick A and Katz L N The effect of atrial depolarization on the response to subthreshold stimulation of the ventricle A preliminary report of clinical and experimental observations in Paired pulse stimulation of the heart Craneheld P F Hoffman B F eds New York 1968 Rockefeller University Press p 32
- Fisch C and Knoebel S B Wenckebach facilitation in the human heart Report of a probable case AM HEART J 76 90 1968
- Castellanos A Jr and Lemberg L Electrophysiology of pacing and cardioversion New York 1969 Appleton Century Crofts Chapter 5 p 134
- Parsonnet V Furman S and Smyth N P D Implantable cardiac pacemakers status report and resource guideline Pacemaker study group Circulation 50 A 21 1974
- Kastor J A and Leimbach H C Pacemakers and their arrhythmias Progr Cardiovasc Dis 13 240 1970
- Fisch C and Greenspan H Editorial Wenckebach's observations Circulation 35 819 1967
- Scherf D and Schott A Extrasystoles and allied arrhythmias Chicago 1973 Year Book Medical Publishers Inc chapter 16 p 1016
- Craneheld P F and Hoffman B F Conduction of the cardiac impulse II Summation and inhibition Circ Res 28 220 1971
- Bailey J C Spear J F and Moore E N Microelectrode demonstration of Wenckebach facilitation in canine cardiac Purkinje fibers Circ Res 33 48 1973
- Wenckebach J H Bandura J P and Ruesta V J Wenckebach facilitation in canine right bundle branch J Electrocardiol 8 285 1973
- Klein H Craneheld P F and Hoffman B F Letter to Editor Wenckebach inhibition AM HEART J 84 717 1972
- Bigger J T Jr Electrical properties of cardiac muscle and possible causes of cardiac arrhythmias in Cardiac arrhythmias Dreifus, L S and Lickoff W eds New York 1973 Grune & Stratton Inc p 13
- Narula O S Current concepts of atrioventricular block in His bundle electrocardiography and clinical electrophysiology Narula O S ed Philadelphia 1975 F A Davis Company chapter 9 p 139
- Preston T A Letter Late supernormal excitation, Am J Cardiol 38 403 1976
- Jochim K The contribution of the auricles to ventricular filling in complete heart block Am J Physiol 122 639 1938
- Brockman S K Dynamic function of atrial contraction in regulation of cardiac performance Am J Physiol 204 597 1963
- Brockman S K and Manlove A Cardiodynamics of complete heart block Am J Cardiol 16 72 1963
- Mitchell J H Gupta D N and Payne R M Influence of atrial systole on effective ventricular stroke volume Circ Res 17 11 1965
- Escher D J W Schwedell J H Schwartz L S and Solomon N Transvenous electrical stimulation of the heart—II Ann N Y Acad Sci 111 981 1964
- Benchumol A Duenas A Liggett M S and Dimond, E G Contribution of atrial systole to the cardiac function at a fixed and at a variable ventricular rate Am J Cardiol 16 11 1965
- Palmero H A Complete heart block and the role of atrial activity AM HEART J 70 449 1965
- Carleton R A Passovoy M and Greeting J S The importance of the contribution and timing of left atrial systole Clin Sci 30 161 1966
- Gillespie W J Greene D G Karatzas, N B and Lee G de J Effect of atrial systole on right ventricular stroke output in complete heart block Br Med J 1 3 1967
- Bashour T T Naughton J P and Cheng T O Systolic time intervals in patients with artificial pacemakers Am J Cardiol 32 287 1973
- Ehlikum M Sapoznikov D and Weinman J Assessment of the atrial contribution to cardiac performance by a noninvasive photoplethysmographic technique Cardiology 58 7 1973
- Igarashi M and Ayabe T Letter Late supernormal excitation Am J Cardiol 38 403 1976
- Abernathy W B Ferner G R and Moe G K The influence of atrial systole on ventricular capture by failing artificial pacemakers II Experimental observations AM HEART J (In press)
- Braunwald E Fishman A P and Courmand A Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man Circ Res 4 160, 1956
- Braunwald E and Frahm C J Studies on Starling's law of the heart IV Observations on the hemodynamic functions of the left atrium in man Circulation 24 631, 1961
- Tavel M E Clinical phonocardiography and external pulse recording Chicago 1972 Year Book Medical Publishers Inc pp 41 186
- Tafur E Cohen L S and Levine H D The normal apex cardiogram Its temporal relationship to electrical, acoustic and mechanical cardiac events Circulation 30 381 1964
- Benchumol A and Dimond E G The normal and abnormal apexcardiogram Its physiologic variation and its relation to intracardiac events Am J Cardiol 32 399 1963
- Benchumol A and Dimond E G The apexcardiogram in normal older subjects and in patients with arteriosclerotic heart disease Effect of exercise on the "a" wave AM HEART J 65 789 1963

## A discussion on hypertrophic cardiomyopathy

Thomas L. Spray MD  
Barry J. Maron MD  
Andrew G. Morrow MD  
Stephen E. Epstein MD  
William C. Roberts MD  
*Bethesda Md*

**DR ROBERTS** The purpose of this conference is to discuss certain clinical, operative and morphologic features of hypertrophic cardiomyopathy as exemplified in one patient. Dr Spray will present the patient.

**DR SPRAY** R. H. (11/65/60-4) a 56 year old white woman was not suspected of having heart disease until she was 30 years old when a precordial murmur was heard. She was in good health until age 40 when she developed angina pectoris and palpitations. From age 51 on her symptoms increased in frequency and severity. In addition she developed orthopnea and paroxysmal nocturnal dyspnea. During the year before death occasional syncopal and presyncopal episodes occurred. In February 1976 she was admitted to a local hospital where an electrocardiogram showed left ventricular hypertrophy with the strain pattern. A treadmill exercise tolerance test was attempted but it was stopped when she developed paroxysmal atrial tachycardia. Cardiac catheterization disclosed the following pressures (in mm Hg): right ventricle (body) 50/3; right ventricle (subpulmonic area) 21/3; pulmonary trunk 21/17 (mean 12); pulmonary arterial wedge mean 7; left ventricle (body) 235/0-25; left ventricle (subaortic area) 105/12; and aorta 105/60 (mean 80). The peak systolic pressure gradient between left ventricle and aorta was 130 mm Hg. The cardiac output was 4.7 liters per minute and the cardiac index 3.0 liters/minute/M. She was

begun on propranolol (160 mg per day) and quinidine.

In May 1976 she was admitted to a local hospital for treatment of severe headache at which time diastolic blood pressures to 130 mm Hg were noted. Diazoxide therapy resulted in marked hypotension which required intravenous metaraminol for stabilization. She was admitted to the National Heart, Lung and Blood Institute 19 days before death.

On examination the blood pressure was 120/80 mm Hg, heart rate 56 per minute and respiratory rate 12 per minute. The jugular venous pulse was normal. The carotid arterial upstroke was judged to be rapid. The lung fields were clear to auscultation. The point of maximal cardiac impulse was in the sixth left intercostal space in the anterior axillary line and the apical beat had a triple character. The first and second heart sounds were normal. A fourth heart sound was present at the apex. A Grade 4/6 systolic ejection type murmur was heard, loudest at the apex and it radiated to the base. The murmur increased in intensity on standing but did not change with Valsalva maneuver. Neither liver nor spleen were palpated but mild pedal edema was noted. **DR ROBERTS:** Dr Maron, could you describe the electrocardiogram, chest roentgenogram and echocardiogram?

**DR MARON:** The electrocardiogram shows left ventricular hypertrophy with strain pattern (Fig 1). In addition the T waves in Leads I and aVL are deeply inverted in a symmetric fashion. ST segments are elevated in Leads V<sub>1</sub> and V<sub>2</sub> and depressed in Leads V<sub>5</sub> and V<sub>6</sub>. Left atrial enlargement also is evident. The chest radiograph shows pectus excavatum, left ventricular enlargement,

From the Pathology, Cardiology and Surgery Branches, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Md.

Received for publication May 3, 1977.

Reprint requests: William C. Roberts, M.D., Bldg 10A, Room 3E-30, NIH, Bethesda, Md. 20814.

trocardiogram, *AM HEART J* 93 629, 1977) Figs 5 through 9 in that article illustrate several clinical cases. In one case, fluoroscopy confirmed movement of the pacing catheter induced by atrial systole.

## REFERENCES

- Dreifus L S Chapter 11 in Current concepts of cardiac pacing and cardioversion Meltzer L R and Kitchell J R eds Philadelphia 1971 The Charles Press p 217
- Sanz G Van Loon G R and Schwartz L Phasic pacemaker failure *J Electrocardiol* 6 267 1973
- Preston T A Atrial phasic inhibition of implanted cardiac pacemakers (Abstract) *Circulation* 37 and 38 (Suppl VI) 158 1968
- Danzig R and Diamond G Increase in threshold to ventricular activation related to atrial contraction A possible example of Wenckebach inhibition *AM HEART J* 82 531 1971
- Soloff L A and Fewell J W The supernormal phase of ventricular excitation in man Its bearing on the genesis of ventricular premature systoles and a note on atrioventricular conduction *AM HEART J* 59 869 1960
- Igarashi M and Ayabe T Quantitative study of the supernormal phase of ventricular excitability in man *Am J Cardiol* 36 292 1975
- Arbel E R Langendorf R Pick A and Katz L N The effect of atrial depolarization on the response to subthreshold stimulation of the ventricles A preliminary report of clinical and experimental observations in paired pulse stimulation of the heart Cranefield P F Hoffman B F eds New York 1968 Rockefeller University Press p 32
- Fisch C and Knoebel S B Wenckebach facilitation in the human heart Report of a probable case *AM HEART J* 76 90 1968
- Castellanos A Jr and Lemberg L Electrophysiology of pacing and cardioversion New York 1969 Appleton Century Crofts Chapter 5 p 134
- Parsonnet V Furman S and Smyth N P D Implantable cardiac pacemakers status report and resource guideline Pacemaker study group *Circulation* 50 A 21 1974
- Kastor J A and Lembach R C Pacemakers and their arrhythmias *Progr Cardiovasc Dis* 13 240 1970
- Fisch C and Greenspan K Editorial Wenckebach's observations *Circulation* 35 819 1967
- Scherf D and Schott A Extrasystoles and allied arrhythmias Chicago 1973 Year Book Medical Publishers Inc chapter 16 p 1016
- Cranefield P F and Hoffman B F Conduction of the cardiac impulse II Summation and inhibition *Circ Res* 28 220 1971
- Bailey J C Spear J F and Moore E N Microelectrode demonstration of Wenckebach facilitation in canine cardiac Purkinje fibers *Circ Res* 33 48 1973
- Wennemark J R Bandura J P and Ruesta V J Wenckebach facilitation in canine right bundle branch *J Electrocardiol* 6 285 1973
- Klein H Cranefield P F and Hoffman B F Letter to Editor Wenckebach inhibition *AM HEART J* 84 717 1972
- Bigger J T Jr Electrical properties of cardiac muscle and possible causes of cardiac arrhythmias in Cardiac arrhythmias, Dreifus L S and Likoff W eds New York, 1973 Grune & Stratton Inc p 13
- Narula O S Current concepts of atrioventricular block in His bundle electrocardiography and clinical electrophysiology Narula O S ed Philadelphia 1975 F A Davis Company chapter 5 p 139
- Preston T A Letter Late supernormal excitation *Am J Cardiol* 38 403 1976
- Jochum K The contribution of the auricles to ventricular filling in complete heart block *Am J Physiol* 122 639 1938
- Brockman S K Dynamic function of atrial contraction in regulation of cardiac performance *Am J Physiol* 204 597 1963
- Brockman S K and Manlove A Cardiodynamics of complete heart block *Am J Cardiol* 16 79 1965
- Mitchell J H Gupta D N and Payne R M Influence of atrial systole on effective ventricular stroke volume *Circ Res* 17 11 1965
- Escher D J W Schwedel J H Schwartz L S and Solomon N Transvenous electrical stimulation of the heart—II *Ann N Y Acad Sci* 111 981 1964
- Benchimol A Duenas A Liggett M S and Diamond E G Contribution of atrial systole to the cardiac function at a fixed and at a variable ventricular rate *Am J Cardiol* 16 11 1965
- Palmero H A Complete heart block and the role of atrial activity *AM HEART J* 70 449 1965
- Carleton R A Passovoy M and Graettinger J S The importance of the contribution and timing of left atrial systole *Clin Sci* 30 151 1966
- Gillespie W J Greene D H Karatzas N B and Lee G de J Effect of atrial systole on right ventricular stroke output in complete heart block *Br Med J* 1 5, 1967
- Bashour T T Naughton J P and Cheng T O Systolic time intervals in patients with artificial pacemakers *Am J Cardiol* 32 287 1973
- Eliakim M Sapoznikov D and Weinman J Assessment of the atrial contribution to cardiac performance by a noninvasive photoplethysmographic technique *Cardiology* 58 7 1973
- Igarashi M and Ayabe T Letter Late supernormal excitation *Am J Cardiol* 38 403 1976
- Abernathy W S Ferner G H and Moe G K The influence of atrial systole on ventricular capture by failing artificial pacemakers II Experimental observations *AM HEART J* (In press)
- Braunwald E Fishman A P and Courmand A Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man *Circ Res* 4 100 1956
- Braunwald E and Frahm C J Studies on Starling's law of the heart IV Observations on the hemodynamic functions of the left atrium in man *Circulation* 24 633, 1961
- Tavel M E Clinical phonocardiography and external pulse recording Chicago 1972 Year Book Medical Publishers Inc pp 41 185
- Tafur E Cohen L S and Levine H D The normal apex cardiogram Its temporal relationship to electrical, acoustic and mechanical cardiac events *Circulation* 30 381 1964
- Benchimol A and Diamond E G The normal and abnormal apex cardiogram Its physiologic variation and its relation to intracardiac events *Am J Cardiol* 12 304 1963
- Benchimol A and Diamond E G The apex cardiogram in normal older subjects and in patients with arteriosclerotic heart disease Effect of exercise on the "a" wave *AM HEART J* 65 789 1963

was noted and no systolic thrill was palpated in the right ventricle at the end of the procedure. The patient came off bypass easily. DR ROBERTS: Dr Morrow, what occurred in the postoperative period?

DR MORROW: The patient was hemodynamically stable throughout the first postoperative day and the first postoperative electrocardiogram showed sinus rhythm and a left bundle branch block pattern. The latter is very common after this operation. On the first postoperative day, however, she developed junctional bradycardia and she was paced via a temporary pacemaker wire which had been implanted at operation. Supraventricular and junctional tachyarrhythmias followed but ultimately sinus rhythm returned. No electrocardiographic changes suggestive of acute myocardial infarct occurred. Because of the supraventricular irritability, propranolol was reinstituted. On the following day a new precordial murmur with an accompanying thrill was noted at the apex and left sternal border. It was holosystolic and Grade 4/6 in intensity. On the following day her ventricular rate suddenly decreased to less than 40 beats per minute. The pacemaker failed to capture the ventricle and she died.

DR ROBERTS: Dr Spray, could you describe the findings at necropsy?

DR SPRAY: At necropsy the heart weighed 680 grams (Figs 5 and 6). (The patient weighed 54.5 kilograms.) Considerable hemorrhage was present in the atrial septum. The tricuspid valve was normal except that its anterior leaflet appeared more elongated than usual. The wall of the right ventricle measured up to 1.3 cm in thickness. The pulmonic valve was normal. Both atria were quite dilated. Both mitral valve leaflets were thickened by fibrous tissue. The left ventricular cavity was small. Measurements of the thickness of the left ventricular myocardium were made at the level at which the ultrasound beam would theoretically pass during life: i.e. between the papillary muscles at the level of the distal margins of the mitral leaflets and at the midpoint of the posterior mitral leaflet. At this level (the echo area) the ventricular septum measured 25 mm and the posterobasal left ventricular free wall 25 mm in maximal thickness. The posterobasal portion of left ventricular free wall was thick and rounded, typical of the configuration observed in patients with left ventricular outflow obstruction at rest.

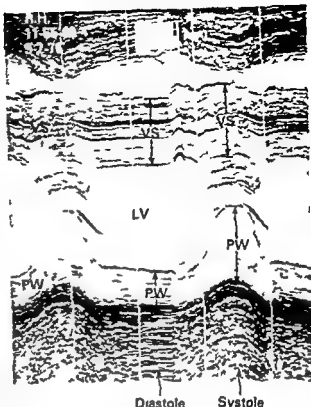


Fig 3 Echocardiogram of present patient showing disproportionate thickening of the ventricular septum (VS) with respect to the posterobasal left ventricular wall (PW) in diastole. In contrast concentric ventricular wall thickening is present in systole. LV = left ventricular cavity.

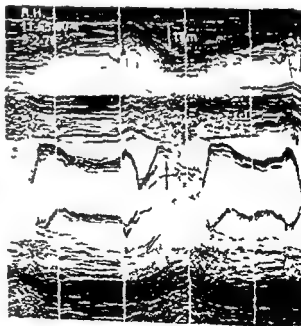
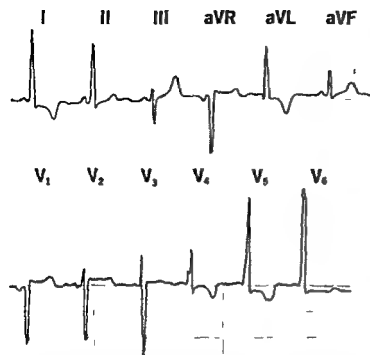


Fig 4 Echocardiogram of present patient showing systolic anterior motion of the anterior mitral leaflet (arrow).





RH  
8-16-78

Fig 1 Preoperative electrocardiogram of present patient showing left ventricular hypertrophy with strain pattern, left atrial enlargement, and ST-segment and T-wave abnormalities.

and normal pulmonary vascular markings (Fig 2). Echocardiogram shows (in diastole) ventricular septal thickness of 24 mm, posterobasal left ventricular wall thickness of 16 mm, and a septal to free wall ratio of 1.5. When wall thicknesses are measured in systole, however, the ventricular septum is 26 mm, the posterobasal left ventricular wall is 29 mm, and hence, the septal to free wall ratio in systole is 0.9 (Fig 3). In addition, marked systolic anterior motion of the anterior mitral leaflet, indicative of severe obstruction to left ventricular outflow, is evident (Fig 4). The transverse internal dimensions of the left ventricle (43 mm) and left atrial (38 mm) cavities and the aortic root (32 mm) were within normal limits.

DR ROBERTS: Dr Epstein, what were your reasons for recommending operation in this patient?

DR EPSTEIN: This patient was considered an ideal candidate for septal myotomy-myectomy for the following reasons: (1) she was severely limited (New York Heart Association, Functional Class III) by extreme fatigue and dyspnea with exertion and in addition she had numerous episodes of syncope and lightheadedness; (2) these symptoms were not lessened significantly



Fig 2 Posteroanterior chest radiograph in present patient showing mild cardiac enlargement and normal pulmonary vascular markings.

by treatment with propranolol; (3) a marked (130 mm Hg) peak systolic pressure gradient was present in the left ventricular outflow tract under basal conditions; (4) there was evidence by echocardiography of a markedly thickened ventricular septum that would permit an adequate myectomy to be performed; and (5) no other major medical problems were identified that would contraindicate a major cardiac operation.

DR ROBERTS: Dr Morrow, could you describe what you found at operation in this patient and the operative procedure you performed?

DR MORROW: The operation performed was the ventricular myotomy and myectomy, which has been used in this institution with minor modifications for 17 years. With the patient on cardiopulmonary bypass, the aorta was opened. After gently retracting the aortic valve cusps, the thickened ventricular septum was observed. Two longitudinal parallel incisions were made in the ventricular septum. The incisions extended caudally from just below the commissure between the right and left aortic valve cusps. The incisions were then joined transversely and the resulting wedge of myocardium was excised. After this procedure, the ventricular septum was palpated and noted to be somewhat thinner than in most patients after this operation. The aortotomy incision was closed. No aortic regurgitation

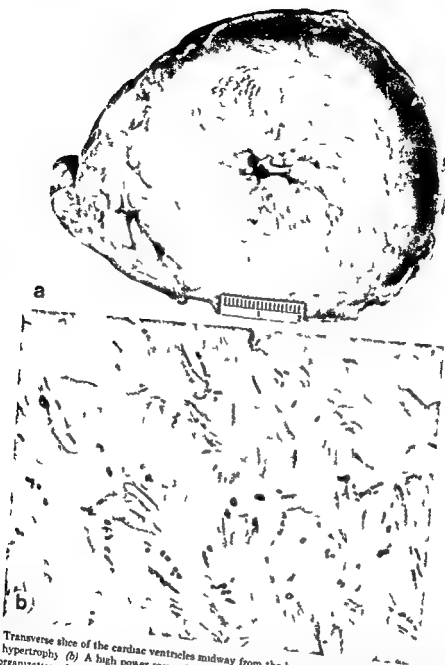


Fig 6 (a) Transverse slice of the cardiac ventricles midway from the base to the apex showing concentric left ventricular hypertrophy (b) A high power view of a portion of myocardium from ventricular septum showing marked disorganization of cells and myofibrillar elements (Hematoxylin and eosin stain original magnification x330)

The myocardium adjacent to the site where the drain was inserted at operation in the apex of left ventricle was necrotic. The edges of the area of operatively excised ventricular septum were necrotic. The most cephalad aspect of this excision extended all the way through the ventricular

septum creating a slit like ventricular septal defect 1 cm long. There were no areas of myocardial fibrosis. The aortic valve was normal anatomically. The epicardial coronary arteries were grossly normal. Histologic examination of the left ventricular septum showed marked disor

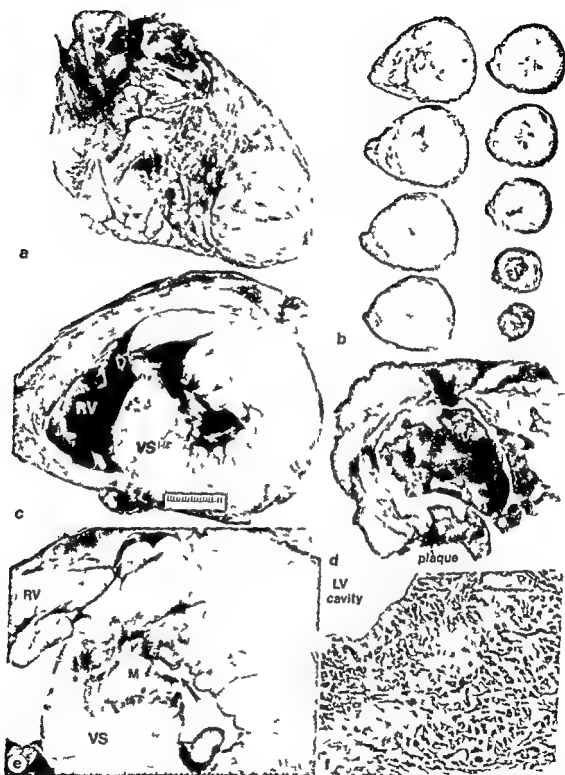
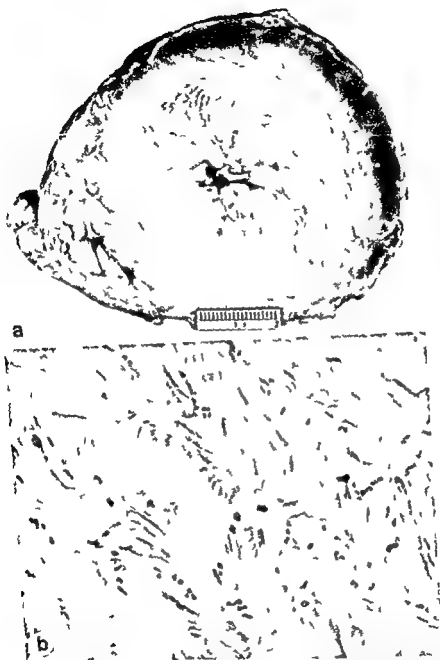


Fig 5 a through f (a) Anterior view of the heart at necropsy showing marked left ventricular prominence (b) Serial slices of the cardiac ventricles from base to apex showing severe left ventricular hypertrophy Hemorrhagic necrosis is present in the apical slices due to its being the site of insertion of the left ventricular drain at operation (c) View of the base of the heart from below showing the area of excision of muscle (arrow) from the left ventricular septum (VS) The site of rupture of the septum with creation of a ventricular septal defect (arrow) is shown RV = right ventricle (d) The left ventricular septal muscle excised at operation showing an endocardial fibrous plaque consistent with a contact lesion from the anterior mitral leaflet The excised muscle weighed 41 grams (e) Close up of a basal slice of the cardiac ventricles showing the myectomy site (arrow) and the surrounding area of necrosis (M) (f) Histologic section of an area of VS adjacent to the myectomy incision showing marked disorganization of myocardial cells and necrosis (Hematoxylin and eosin stain original magnification  $\times 80$ )



**Fig 1** (a) Transverse slice of the cardiac ventricles midway from the base to the apex showing concentric left ventricular hypertrophy (b) A high power view of a portion of myocardium from ventricular septum showing marked disorganization of cells and myofibrillar elements. (Hematoxylin and eosin stain original magnification  $\times 330$ )

The myocardium adjacent to the site where the drain was inserted at operation in the apex of left ventricle was necrotic. The edges of the area of operatively excised ventricular septum were necrotic. The most cephalad aspect of this excision extended all the way through the ventricular

septum creating a slit like ventricular septal defect 1 cm long. There were no areas of myocardial fibrosis. The aortic valve was normal anatomically. The epicardial coronary arteries were grossly normal. Histologic examination of the left ventricular septum showed marked disor

ganization of myocardial fibers and coagulation necrosis of myocardium bordering the myotomy and myectomy incision (Figs 5 and 6) The intramural coronary arteries in the ventricular septum were normal

DR ROBERTS Dr Epstein patients with hypertrophic cardiomyopathy often have chest pain occasionally clear angina pectoris just like patients with valvular aortic stenosis What is the cause of angina pectoris in patients with hypertrophic cardiomyopathy? Do they have associated coronary arterial narrowing due to atherosclerosis or is there another cause for the angina pectoris? Or is it really angina pectoris?

DR EPSTEIN It is true that many patients with hypertrophic cardiomyopathy or ASH, have chest pain or discomfort indistinguishable from that of typical angina pectoris Since coronary artery disease is relatively common it is not surprising to find that the two diseases occasionally coexist in a given patient In such patients the coronary artery disease undoubtedly contributes to the chest pain syndrome However, in the large majority of patients with hypertrophic cardiomyopathy chest discomfort occurs without any coronary arterial abnormality discernible by coronary angiography or at necropsy In patients with obstruction to left ventricular outflow (who consequently have high intraventricular pressures) angina probably occurs because of the excessively high myocardial oxygen consumption, i.e., myocardial oxygen demands outstrip the capacity of the coronary arteries to deliver oxygen just as in patients with aortic stenosis In patients without obstruction the origin of the patient's chest pain is unclear It may be that proliferation of myocardial capillaries has not kept pace with the excessive amount of hypertrophy present in these patients

DR ROBERTS Dr Epstein what is the cause of syncope or presyncope in patients with hypertrophic cardiomyopathy? Is syncope more frequent in the patients with obstruction to left ventricular outflow at rest or is it just as frequent in patients without obstruction either at rest or with provocation?

DR EPSTEIN Syncope and presyncope occur commonly in patients with obstruction to left ventricular outflow as well as in patients without obstruction to left ventricular outflow This fact suggests that while syncope in patients with hypertrophic cardiomyopathy may be due to an

abrupt increase in the magnitude of left ventricular outflow obstruction in some patients other mechanisms also must be operative One such mechanism that can lead to syncope and presyncope in patients with hypertrophic cardiomyopathy is a ventricular arrhythmia Supportive evidence for this conclusion is the documentation of ventricular fibrillation just after collapse in a few patients observed by us and other investigators It should also be emphasized that although syncope and presyncope are common in patients with obstructive hypertrophic cardiomyopathy these symptoms do not have the same alarming connotation in such patients as they would in patients with fixed valvular aortic stenosis We have for example, followed many patients for over 10 years with such symptoms Such a benign course would be unheard of in a patient with syncope associated with valvular aortic stenosis Hence, we do not recommend operation to relieve obstruction in patients with hypertrophic cardiomyopathy on the basis of syncope or presyncope alone On the other hand, we have evaluated some patients who have died suddenly with no symptomatology before death other than a single episode of syncope or occasional presyncope Hence it is possible that syncope can be the first manifestation of cardiac disease before sudden death in patients with hypertrophic cardiomyopathy

DR ROBERTS Dr Epstein, I understand a number of patients with hypertrophic cardiomyopathy with or without obstruction have exertional dyspnea How many patients with this condition actually have overt evidence of congestive heart failure or to put it another way is congestive heart failure in the patient with hypertrophic cardiomyopathy similar to congestive heart failure in patients with other cardiac conditions? Morphologically hypertrophic cardiomyopathy is one of the conditions in which congestive heart failure occurs and yet, neither congestive heart failure nor dilated Among the few conditions in which congestive cardiac failure occurs and the ventricular cavities are not dilated are amyloidosis mitral stenosis hemochromatosis and constrictive pericarditis Is there anything different clinically about the congestive heart failure in patients with hypertrophic cardiomyopathy compared to that occurring in patients with other cardiac conditions?

DR EPSTEIN Patients with hypertrophic cardio

myopathy may demonstrate many of the clinical manifestations we interpret as indicative of congestive heart failure. The mechanism of failure, however, is probably different in this condition than in patients with acquired valvular heart disease. For example, patients with hypertrophic cardiomyopathy have a poorly compliant left ventricle. This is due presumably to the markedly thickened ventricular walls. This stiffened ventricle results in restriction to left ventricular filling, i.e., left ventricular inflow obstruction. As a result, left atrial and pulmonary venous pressures increase and consequently may lead to clinical manifestations of left and right sided heart failure. This occurs despite preservation of systolic function, at least as assessed at rest. Many patients with either the obstructive or the non-obstructive form of the disease may manifest these findings. In fact, in the latter stages of non-obstructive hypertrophic cardiomyopathy, patients may present with a picture very similar to that of congestive or dilated cardiomyopathy, with the exception that the ventricular cavities do not dilate. On the other hand, (1) we and others have observed a small number of patients with non-obstructive hypertrophic cardiomyopathy who in the end stages of their disease manifest impaired systolic function (normal end diastolic volume with decreased ejection fraction) and (2) a very few patients have shown mild enlargement of the left ventricular cavity in end-diastole. The most characteristic picture of end-stage disease in non-obstructive hypertrophic cardiomyopathy, however, is inflow obstruction and preservation of systolic function.

**DR ROBERTS:** The present patient had historical evidence of systemic hypertension on one or more occasions, although the blood pressure recordings at NIH were normal. Dr. Maron, how often does systemic hypertension occur in patients with hypertrophic cardiomyopathy, and how often do patients with systemic hypertension have echocardiographic or morphologic evidence of hypertrophic cardiomyopathy?

**DR MARON:** One of the first concepts of hypertrophic cardiomyopathy was that the subaortic muscular stenosis was due to preexisting systemic hypertension, probably because some of the first patients described with this condition nearly 20 years ago just happened to have coexistent systemic hypertension. Subsequently, we have

come to realize that hypertension is not common in patients with hypertrophic cardiomyopathy. Hence, there is very little evidence for a causal relation between the two conditions. Looking at this question in another way, we have studied by echocardiography and at necropsy over 300 patients with systemic hypertension and found disproportionate septal thickening in about 5 per cent. Furthermore, the disproportionate septal thickening in patients with systemic hypertension does not appear to be genetically transmitted but rather secondary to the patient's particular hemodynamic state—i.e., systemic hypertension. Hence, systemic hypertension is uncommon in patients with hypertrophic cardiomyopathy and disproportionate septal thickening is uncommon in patients with systemic hypertension.

**DR ROBERTS:** The present patient had a loud precordial murmur, and most patients with hypertrophic cardiomyopathy I understand have a precordial murmur. Dr. Maron, do any patients with hypertrophic cardiomyopathy not have a murmur, and when a murmur is present, what is it due to?

**DR MARON:** Actually, in our experience, loud precordial murmurs are rare in the overall population of patients whom we see with hypertrophic cardiomyopathy. This is due principally to the fact that about 75 per cent of the patients who we evaluate with this condition do not have obstruction to left ventricular outflow. If outflow obstruction is absent, then a loud murmur (Grade 3/6 or more) rarely, if ever, is present. In patients with obstruction to left ventricular outflow (such as the patient discussed here), a loud systolic ejection murmur is almost invariably present along the left sternal border and at the apex. These statements, however, have to be tempered by the fact that the left ventricular outflow gradient in hypertrophic cardiomyopathy is extremely labile and may be present or absent from beat to beat, hour to hour, or day to day. Therefore, the presence or absence of a precordial murmur or its intensity at any one point in time cannot be used as definitive evidence of obstruction to outflow.

**DR ROBERTS:** Thus, a patient with a loud precordial systolic murmur and hypertrophic cardiomyopathy, with rare exception, has obstruction to left ventricular outflow. What happens to the systolic precordial murmur after adequate myotomy or myectomy?

**DR MARON** The precordial murmur in patients with hypertrophic cardiomyopathy is mainly related to systolic anterior motion of the mitral valve, which results in outflow obstruction and often mitral regurgitation. Since myotomy-myectomy almost invariably obliterates the resting gradient in these patients, the murmur either disappears or is markedly diminished in intensity.

**DR ROBERTS** Although a few patients with hypertrophic cardiomyopathy have obstruction not only to left ventricular outflow but also to right ventricular outflow, I wonder, Dr Maron, what the explanation for the right ventricular outflow obstruction really is. For example, I am not aware that the ventricular septum is any thicker in patients with right ventricular outflow obstruction than in patients with no obstruction to right ventricular outflow but considerable left ventricular outflow obstruction. Why is not the right ventricular outflow obstruction more common and what is your explanation for the obstruction when it does occur?

**DR MARON** About 20 per cent of our patients with hypertrophic cardiomyopathy and obstruction to left ventricular outflow also have right ventricular outflow tract gradients (usually less than 40 mm Hg). However, a rare patient manifests marked obstruction to right ventricular outflow which is occasionally greater than, or present in the absence of, obstruction to left ventricular outflow. Although the explanation for right ventricular outflow gradients in patients with hypertrophic cardiomyopathy is unclear, it is perhaps most likely that the markedly hypertrophied ventricular septum and/or crista supraventricularis impinges on the right ventricular outflow tract and produces obstruction.

**DR ROBERTS** We have studied 65 patients with hypertrophic cardiomyopathy at necropsy and as I recall only three had obstruction to right ventricular outflow and the largest gradient among the three was 50 mm Hg. In that particular patient the anterior tricuspid valve leaflet was quite elongated, and it appeared possible that the excessive length of the anterior tricuspid valve leaflet located in a small right ventricular cavity was the likely explanation for the obstruction. In the present patient the right ventricular outflow gradient was 29 mm Hg and the anterior tricuspid valve leaflet probably was more elongated than normal. The present patient also had

a very thick crista supraventricularis and an extremely small right ventricular cavity. At necropsy, for example (Figs 5 and 6) the right ventricular free wall virtually contacts the right ventricular aspect of the ventricular septum.

**DR MARON** There appears to be some discrepancy between the thicknesses of the ventricular walls measured at necropsy and during life by echocardiography in this patient. Can you explain these discrepancies?

**DR MARON** Recently we have observed several patients with hypertrophic cardiomyopathy similar in this respect to the patient described in this report.<sup>1</sup> That is the echocardiogram during life showed asymmetric septal hypertrophy but at necropsy concentric hypertrophy was present. In this patient, the echocardiogram showed a septal to free wall ratio of 1.5 in diastole, which met our diagnostic criteria of ASH. However, at necropsy the septal to free wall ratio was 0.9 and therefore not diagnostic of ASH. These discrepancies may be explained as follows. First, in patients with ASH, the ventricular septum thickens less during ventricular systole than does the left ventricular free wall. As a result, septal to free wall ratios are greater when measurements are obtained in diastole than when they are obtained in systole. Second, hearts examined at necropsy appear to be in the systolic phase of the cardiac cycle. This conclusion is suggested by the fact that the ventricular wall thickness, septal to free wall ratios and left ventricular internal transverse dimensions measured at necropsy all correlated more closely with measurements attained echocardiographically in systole than in diastole.<sup>1</sup> Since by convention, echocardiographic measurements of wall thicknesses are made during diastole, it becomes clear why septal to free wall ratios consistent with the diagnosis of hypertrophic cardiomyopathy (ASH) during life may be inconsistent with this diagnosis after death. Hence, we believe that at least occasionally echocardiographic measurements in diastole provide a more sensitive method than necropsy examination for documenting the presence of hypertrophic cardiomyopathy.

The implication of these findings is that in certain patients with typical genetically transmitted hypertrophic cardiomyopathy, the diagnosis will not be established at necropsy by simple measurement of the relative thicknesses of the ventricular septum and left ventricular free wall.

In such patients the correct diagnosis will rely on other ancillary observations including typical hemodynamic and echocardiographic features of left ventricular outflow obstruction during life (as shown in the present patient) and the presence of a documented family history of hypertrophic cardiomyopathy. Other necropsy findings suggestive but not diagnostic of hypertrophic cardiomyopathy include a contact plaque on the endocardium of the ventricular septum in apposition to a thickened anterior mitral leaflet and the presence of numerous hypertrophied and disorganized cardiac muscle cells in the ventricular septum.

**DR ROBERTS:** Dr Maron, on the echocardiographic record are you always sure about the exact location of the epicardial surface of the posterior left ventricular free wall in patients with hypertrophic cardiomyopathy? I would assume that you would be considerably pleased if patients with hypertrophic cardiomyopathy had a little pericardial effusion so that this surface of the free wall would be clearly delineated. Could you comment on how often you feel that you cannot make a precise unequivocal measurement of the posterior free wall by echocardiogram in patients with hypertrophic cardiomyopathy?

**DR MARON:** Dr Roberts' comments about technical considerations in obtaining optimal echocardiograms is certainly well taken. A satisfactory echocardiogram can probably be obtained in 80 to 90 per cent of patients with hypertrophic cardiomyopathy. Nevertheless, there are some important technical points that should always be considered. For example, delineation of the right ventricular surface of the ventricular septum itself is often very difficult in some patients. Furthermore, as Dr Roberts has pointed out, measurement of the posterobasal left ventricular wall is also frequently difficult in these patients with regard to definition of either the endocardial or epicardial surface. In a small minority of patients with clinically evident hypertrophic cardiomyopathy it has not been possible to make a definitive conclusion about the septal to free wall ratio because of these considerations.

**DR ROBERTS:** Dr Morrow, your results with myotomy and myectomy in patients with hypertrophic cardiomyopathy have been quite gratifying with few exceptions. The present patient obviously is one of those exceptions. I understand that you have operated on nearly 200 patients

with hypertrophic cardiomyopathy and that the occurrence of a ventricular septal defect has been quite rare. I wonder if you could comment on your general results with this procedure and your views on the particular operative complications in this particular patient.

**DR MORROW:** I have now operated upon approximately 175 patients with the obstructive form of hypertrophic subaortic stenosis. The operative mortality rate associated with the procedure is similar to that for aortic valve replacement, 5 to 7 per cent. We have had relatively few late deaths due to heart disease and as yet I do not think we can make meaningful comparisons of the natural histories of operated and unoperated patients. Among operative survivors, symptomatic improvement has been quite satisfactory; nearly two thirds of patients consider themselves asymptomatic and the others with few exceptions are in Functional Class II. Ventricular septal defects have occurred in a total of seven patients. Several of them were created and recognized at the time of operation, but it was not considered necessary to close them. One of these patients subsequently had to have the defect closed because he developed heart failure. In the remaining patients, including the patient being discussed here, the ventricular septum ruptured after operation as a consequence of septal infarction. I assume that infarction occurred in these patients because the muscular resection was too extensive and compromised the blood supply of the septum beneath and adjacent to it. We have recently found that intraoperative measurements of the thickness of the septum by means of an intracardiac echo transducer are of aid in gauging the extent of resection necessary.

**DR ROBERTS:** In the present patient 4.1 Gm of ventricular septum was excised at operation. Dr Spray, in the other patients in whom this procedure has been performed by Dr Morrow, how many grams of myocardium were excised from ventricular septum?

**DR SPRAY:** Among 75 specimens the excised muscle ranged in weight from 0.2 to 6.8 grams (average 1.8 Gm).

**DR ROBERTS:** One other anatomic feature of hypertrophic cardiomyopathy is the presence of wall thickening and luminal narrowing of intramural coronary arteries located primarily in the ventricular septum but also occasionally in right ventricular and left ventricular free walls. These



**DR MARON** The precordial murmur in patients with hypertrophic cardiomyopathy is mainly related to systolic anterior motion of the mitral valve, which results in outflow obstruction and often mitral regurgitation. Since myotomy-myectomy almost invariably obliterates the resting gradient in these patients the murmur either disappears or is markedly diminished in intensity.

**DR ROBERTS** Although a few patients with hypertrophic cardiomyopathy have obstruction not only to left ventricular outflow but also to right ventricular outflow I wonder, Dr Maron, what the explanation for the right ventricular outflow obstruction really is. For example, I am not aware that the ventricular septum is any thicker in patients with right ventricular outflow obstruction than in patients with no obstruction to right ventricular outflow but considerable left ventricular outflow obstruction. Why is not the right ventricular outflow obstruction more common and what is your explanation for the obstruction when it does occur?

**DR MARON** About 20 per cent of our patients with hypertrophic cardiomyopathy and obstruction to left ventricular outflow also have right ventricular outflow tract gradients (usually less than 40 mm Hg). However, a rare patient manifests marked obstruction to right ventricular outflow which is occasionally greater than or present in the absence of, obstruction to left ventricular outflow. Although the explanation for right ventricular outflow gradients in patients with hypertrophic cardiomyopathy is unclear it is perhaps most likely that the markedly hypertrophied ventricular septum and/or crista supraventricularis impinges on the right ventricular outflow tract and produces obstruction.

**DR ROBERTS** We have studied 65 patients with hypertrophic cardiomyopathy at necropsy and as I recall only three had obstruction to right ventricular outflow and the largest gradient among the three was 50 mm Hg. In that particular patient the anterior tricuspid valve leaflet was quite elongated, and it appeared possible that the excessive length of the anterior tricuspid valve leaflet located in a small right ventricular cavity was the likely explanation for the obstruction. In the present patient, the right ventricular outflow gradient was 29 mm Hg and the anterior tricuspid valve leaflet probably was more elongated than normal. The present patient also had

a very thick crista supraventricularis and an extremely small right ventricular cavity. At necropsy, for example (Figs 5 and 6) the right ventricular free wall virtually contacts the right ventricular aspect of the ventricular septum.

Dr Maron, there appears to be some discrepancy between the thicknesses of the ventricular walls measured at necropsy and during life by echocardiography in this patient. Can you explain these discrepancies?

**DR MARON** Recently, we have observed several patients with hypertrophic cardiomyopathy similar in this respect to the patient described in this report.<sup>2</sup> That is, the echocardiogram during life showed asymmetric septal hypertrophy but at necropsy concentric hypertrophy was present. In this patient, the echocardiogram showed a septal to free wall ratio of 1.5 in diastole, which met our diagnostic criteria of ASH. However, at necropsy the septal to free wall ratio was 0.9 and therefore not diagnostic of ASH. These discrepancies may be explained as follows. First in patients with ASH the ventricular septum thickens less during ventricular systole than does the left ventricular free wall. As a result, septal to free wall ratios are greater when measurements are obtained in diastole than when they are obtained in systole. Second, hearts examined at necropsy appear to be in the systolic phase of the cardiac cycle. This conclusion is suggested by the fact that the ventricular wall thickness, septal to free wall ratios and left ventricular internal transverse dimensions measured at necropsy all correlated more closely with measurements attained echocardiographically in systole than in diastole. Since by convention echocardiographic measurements of wall thicknesses are made during diastole, it becomes clear why septal to free wall ratios consistent with the diagnosis of hypertrophic cardiomyopathy (ASH) during life may be inconsistent with this diagnosis after death. Hence we believe that at least occasionally echocardiographic measurements in diastole provide a more sensitive method than necropsy examination for documenting the presence of hypertrophic cardiomyopathy.

The implication of these findings is that in certain patients with typical genetically transmitted hypertrophic cardiomyopathy, the diagnosis will not be established at necropsy by simple measurement of the relative thicknesses of the ventricular septum and left ventricular free wall.

## Creatine kinase isoenzymes in the assessment of heart disease

Robert Roberts MD  
Burton E Sobel MD  
St. Louis Mo

Because chest pain and transitory electrocardiographic changes do not differentiate patients with coronary insufficiency from those with myocardial infarction, objective confirmation of myocardial necrosis by analysis of plasma enzymes has assumed increasing importance. Enzymes such as serum glutamic oxalacetic transaminase (SGOT), lactate dehydrogenase (LDH), and creatine kinase (CK)\* may be released into blood from organs besides the heart. However, delineation of isoenzyme profiles improves diagnostic specificity substantially. Since elevated plasma activity of one isoenzyme of CK, MB CK, appears to be the most sensitive and specific enzymatic index of acute myocardial infarction,<sup>1,2</sup> MB CK will be the subject of this selective review.

### Characteristics of creatine kinase and creatine kinase isoenzymes

Creatine kinase is a dimeric molecule with molecular weight of approximately 86,000 daltons, consisting of two subunits of either the B or M type. The M subunit is predominant in skeletal muscle; the B subunit in brain. CK participates in a reversible reaction transferring high energy phosphate from ATP to creatine phosphate. Arginine in each monomer binds the

From the Cardiac Division, Washington University School of Medicine, St. Louis, Mo.

Supported in part by National Institutes of Health Grant HL 17646. SCOR in Ischemic Heart Disease.

Received for publication Feb 18, 1977.

Reprint requests: Burton E. Sobel MD, Director, Cardiac Division, Washington University School of Medicine, 660 So. Euclid Ave., St. Louis, Mo 63110.

Creatine kinase is the preferred term rather than creatine phosphokinase since by definition kinases mediate the transfer of high energy phosphate from substrate to product.

magnesium ATP or ADP complex necessary for the reaction. Each monomer contains one sulfhydryl group necessary for enzymatic activity. Thus a thiol activator is needed to elicit maximal activity *in vitro*.<sup>3</sup> CK dimers are subject to dissociation into subunits particularly when exposed to freezing and thawing or to high concentrations of urea.

Three CK isoenzymes have been recognized in plasma: BB, MM, and MB. Because of the negative charge of the B subunit at pH 8.0, MM is neutral, MB intermediate, and BB most negatively charged and hence most mobile in an electrophoretic field.<sup>4</sup>

Measured CK activity is similar in corresponding serum and plasma samples and not affected by therapeutic concentrations of heparin or coumadin compounds. However, plasma samples should be collected in EGTA rather than EDTA since magnesium required for enzymatic activity may be sequestered by EDTA. Stability of CK during storage varies with the isoenzyme profile in the sample.<sup>5</sup> MM CK collected in EGTA and mercaptoethanol is stable at room temperature for 48 hours, but MB and BB are stable for only 2 hours under these conditions.<sup>10</sup> However, BB and to some extent MB are unstable at room temperature in the absence of a reducing agent, which must be added promptly since loss of activity due to dissociation into subunits cannot be restored completely. With refrigeration, MM is stable for at least 6 days and BB and MB for 24 hours.<sup>6</sup> With fast freezing and storage at -20° or -70° C in the presence of mercaptoethanol and EGTA, MM and MB are stable for years and BB is stable for at least six months.<sup>7</sup>

The half-lives of circulating CK isoenzymes in

abnormal arteries have been observed in about 50 per cent of the 65 patients whom we have studied at necropsy. In the present patient, despite severe left ventricular outflow obstruction, the intramural coronary arteries were normal. We have been unable to correlate the abnormal intramural arteries with the degree of obstruction or the presence of chest pain or any other clinical or hemodynamic parameter. The abnormalities in these arteries, however, are more striking than are observed in any other condition we have studied at necropsy.

# REFERENCES

- 1 Morrow A G, Reitz B A, Epstein S E, Henry W L, Conkle D M, Itskowitz S B and Redwood D H

- Operative treatment in hypertrophic subaortic stenosis. Techniques and the results of pre- and post-operative assessments in 83 patients. *Circulation* 52:68-19-3
- 2 Maron B J, Henry W L, Roberts W C and Epstein S E. Comparison of echocardiographic and necropsy measurements of ventricular wall thickness in patients with and without disproportionate septal thickening. *Circulation* 55:341-1977
- 3 Roberts W C and Ferrans V J. Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types and endomyocardial disease with and without eosinophilia. *Human Pathol* 6:287-1975
- 4 McReynolds R A and Roberts W C. The intramural coronary arteries in hypertrophic cardiomyopathy. (Abstr.) *Am J Cardiol* 35:154-1975

## Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following statement, signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company, in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

Table I Creatine kinase isoenzyme distribution in human skeletal muscle

|                                   | MB<br>isoen % | MM<br>isoen % |
|-----------------------------------|---------------|---------------|
| Van der Veen and Willebrands 1966 | ±             | +++           |
| Dawson and Fine 196               | ±             | +++           |
| Sherwin et al 1967                | ±             | +++           |
| Trainer and Gruening 1968         | —             | +++           |
| Magalhães 1968                    | +             | +++           |
| Kontinen and Somer 1970           | —             | +++           |
| Roe et al 1972                    | —             | +++           |
| Smith 1972 <sup>a</sup>           | ±             | +++           |
| Klein et al 1973                  | —             | +++           |

Legend ± present inconspicuously — absent conspicuously + present consistently

### Results of qualitative CK isoenzyme assays

Plasma CK isoenzymes were first separated on the basis of electric charge. With electrophoresis of samples at alkaline pH MM remains at the origin, BB exhibits the greatest electrophoretic mobility and the mobility of MB is intermediate. Supporting media for electrophoresis include agar, agarose, cellulose acetate and polyacrylamide gel.<sup>1</sup> After separation of the isoenzymes by electrophoresis the supporting medium is incubated with reagents necessary to generate NADPH (detectable by fluorescence or dye reduction) in regions where CK isoenzyme activity is present. When CK isoenzyme profiles were delineated in human tissues with these qualitative techniques brain was found to contain BB and heart MM and MB. However, observations with extracts from skeletal muscle were conflicting (Table I). Although in most studies only MM was detected in skeletal muscle, MB was reported in some as well. In view of limitations of assays based on electrophoretic techniques, stability of CK isoenzymes and recent information obtained with quantitative CK isoenzyme assays, these results must be interpreted with caution. In all but one of the studies postmortem material was used. Since MB is much less stable than MM, it is possible that MB present initially in the tissue could have been overlooked because of tissue autolysis under these circumstances. Since tissue samples were often analyzed after repetitive freezing and thawing, now known to induce conformational changes in the molecule and alteration of electrophoretic mobility, results may have been distorted.

Table II Creatine kinase isoenzyme distribution in human tissue\*

| Tissue   | CA (IU/Gm) | MM         | MB       | BB       |
|----------|------------|------------|----------|----------|
| Muscle   | 3000 ± 200 | 3000 ± 200 | 0        | 0        |
| Heart    | 1600 ± 160 | 170 ± 120  | 730 ± 30 | 0        |
| Brain    | 900 ± 30   | II         | II       | 900 ± 30 |
| GI tract | 140 ± 20   | 0          | 42 ± 1   | 136 ± 20 |
| Adrenal  | 50 ± 6     | II         | 0        | 50 ± 6   |
| Lung     | 13 ± 2     | 1 ± 0.2    | 0        | 12 ± 0.5 |
| Kidney   | 9 ± 2      | 1 ± 0.1    | 0        | 8 ± 0.5  |

Data obtained from references No. 3, 1, 4 and unpublished observations.

Nonspecific fluorescence from moieties other than CK was often not excluded by performing assays both with and without creatine phosphate, the substrate specific for CK. Thus, apparent MB in the skeletal muscle extract may have been an artifact unrelated to any CK isoenzyme. Since electrophoretic scanning techniques are not quantitative, they may have grossly overestimated the amount of MB CK activity present as was the case in early reports of MB CK content in canine myocardium representing as much as 40 per cent of total CK activity,<sup>2</sup> and therefore twentyfold more than the 2 per cent actually present and measurable with quantitative techniques.<sup>1</sup> However, even a small proportion of MB in skeletal muscle could be associated with release of a significant amount of MB into the circulation after intramuscular injections, muscle trauma, surgery or shock, potentially clouding the diagnosis of myocardial infarction. Thus, resolution of the question of how much MB is present in skeletal muscle was needed.

### Results of quantitative CK isoenzyme assays

The kinetic fluorometric quantitative assay for CK isoenzyme developed in 1974<sup>3</sup> had a sensitivity of 2 IU/L and reproducibility of ± 3 per cent. Human tissues removed at the time of surgery and extracted immediately prior to freezing were assayed with this technique both with and without creatine phosphate to exclude apparent activity from moieties other than CK.<sup>4</sup> As shown in Table II, myocardium was found to contain predominantly MM with MB representing approximately 15 per cent of total CK activity. Skeletal muscle analyzed included deltoid, pectoralis major and minor, gastrocnemius and rectus abdominus, all of which contained MM, CK.

*in vivo* are 10 to 12 hours (MM) and 6 to 8 hours (MB). BB appears only rarely in plasma in part because of an apparently short half life.<sup>11</sup>

Since the development of Rosalki's modification of the original Ohver assay for total CK activity,<sup>3</sup> uniform and reproducible results have been obtained with the back reaction in which creatine phosphate is converted to ATP. Reagents required are supplied from several manufacturers in kit form and provide reliable results as long as reasonable precautions are taken for quality control. Activity is expressed in international units/liter with 1 IU defined as the activity required to convert 1  $\mu$ mole of substrate to 1  $\mu$ mole of product under reaction conditions at 30°C. With assays performed at 30°C (the temperature recommended by the International Union of Biochemists), the upper limit of normal for total CK is 65 IU/L and 50 IU/L for male and female subjects.

Although some CK activity is present in most human tissues obtained surgically (as opposed to necropsy specimens), appreciable quantities are found in only four.<sup>12</sup> Skeletal muscle is the most richly endowed source with 3200 IU/Gm. Human myocardium contains 1600 IU/Gm, brain 200 IU/Gm, and gastrointestinal tract approximately 150 IU/Gm. Other tissues such as lung (13 IU/Gm), spleen and liver (< 1 IU/Gm), and kidney (13 IU/Gm) contain almost negligible amounts. No CK is detectable in human erythrocytes.

#### **Plasma CK as an index of myocardial infarction**

Elevated CK activity as a criterion of myocardial infarction was first described by Dreyfus and co-workers in 1960<sup>13</sup> and found soon after to be a sensitive index of acute myocardial injury with positive results in 95 to 100 per cent of patients.<sup>14-16</sup> Results of studies with large numbers of patients with comparison of several enzymatic indices indicated that CK was the most sensitive.<sup>11-13</sup>

Total plasma CK activity generally increases 4 to 8 hours after the onset of chest pain, peaks within 12 to 24 hours, and returns to within the normal range within 72 to 96 hours.<sup>3</sup> However, despite its sensitivity, elevation of total plasma CK activity lacks specificity for the diagnosis of acute myocardial infarction with a false positive incidence of approximately 15 per cent.<sup>14</sup> This is not surprising since total plasma CK activity increases in association with many noncardiac

disorders including muscular dystrophy, inflammatory disease of muscle, trauma or intramuscular injections (particularly of morphine, phenothiazines, and barbiturates even without overt signs of injury), cerebral disease, alcohol intoxication, diabetes mellitus with and without ketosis, convulsions, and psychosis—often due to CK release from skeletal muscle. In addition, increases in plasma CK occur with shock, myxedema, pulmonary embolism, pneumonia, radiotherapy, chronic lung disease, surgery, and exercise.<sup>16-18</sup>

High concentrations of barbiturates, valium, morphine, and anesthetics decrease the rate of disappearance of CK from the circulation in experimental animals and may therefore be associated with elevated plasma CK even under conditions in which release is not augmented.<sup>11</sup> Increases have been seen as well after oral administration of aminocaproic acid, clofibrate, carbenoxolone, imipramine, and glutethimide.<sup>11,19</sup>

Several cardiac conditions besides myocardial infarction may give rise to elevated total plasma CK activity. Although plasma CK does not generally increase in patients with mild congestive heart failure, it may in patients with pulmonary edema and severe hepatic congestion.<sup>20</sup> Pericarditis, myocarditis, electrical cardioversion, and cardiac catheterization may lead to increased CK dependent upon CK release from skeletal muscle or other organs besides the heart.<sup>21</sup>

#### **Plasma CK isoenzymes and myocardial infarction**

Beginning in 1966, analysis of plasma CK isoenzyme profiles was utilized to provide more specific diagnostic information regarding myocardial infarction.<sup>3</sup> However, technical limitations precluded general use of this approach until much later despite progress by Sherwin and associates,<sup>22</sup> Trainer and colleagues,<sup>23</sup> and others.<sup>24-26</sup> Quantitative analysis of CK isoenzyme profiles in human tissues necessary to establish both diagnostic specificity and sensitivity of elevated plasma MB CK was hampered by lack of quantitative techniques<sup>27</sup> for assay of plasma CK isoenzymes until recently when a kinetic fluorometric technique was developed.<sup>28</sup> Although laborious, this method served as a useful standard for development of more convenient approaches and facilitated delineation of tissue isoenzyme profiles.

**Table I** Creatine kinase isoenzyme distribution in human skeletal muscle

|                                   | MB<br>isoenzyme | MM<br>isoenzyme |
|-----------------------------------|-----------------|-----------------|
| Van der Veen and Willebrands 1966 | ±               | +++             |
| Dawson and Fine 1961              | ±               | +++             |
| Sherwin et al 1967                | ±               | +++             |
| Trainer and Gruening 1968         | —               | +++             |
| Magalhaes 1967                    | +               | +++             |
| Kontinen and Somer 1972           | —               | +++             |
| Roe et al 1973                    | —               | +++             |
| Smith 1974                        | ±               | +++             |
| Klem et al 1973                   | —               | +++             |

Leg: nd = present inconsistently; — = absent consistently; + = present consistently

### Results of qualitative CK isoenzyme assays

Plasma CK isoenzymes were first separated on the basis of electric charge. With electrophoresis of samples at alkaline pH MM remains at the origin BB exhibits the greatest electrophoretic mobility and the mobility of MB is intermediate. Supporting media for electrophoresis include agar, agarose, cellulose acetate, and polyacrylamide gel. After separation of the isoenzymes by electrophoresis the supporting medium is incubated with reagents necessary to generate NADPH (detectable by fluorescence or dye reduction) in regions where CK isoenzyme activity is present. When CK isoenzyme profiles were delineated in human tissues with these qualitative techniques brain was found to contain BB and heart MM and MB. However, observations with extracts from skeletal muscle were conflicting (Table I). Although in most studies only MM was detected in skeletal muscle, MB was reported in some as well. In view of limitations of assays based on electrophoretic techniques, stability of CK isoenzymes, and recent information obtained with quantitative CK isoenzyme assays, these results must be interpreted with caution. In all but one of these studies postmortem material was used. Since MB is much less stable than MM, it is possible that MB present initially in the tissue could have been overlooked because of tissue autolysis under these circumstances. Since tissue samples were often analyzed after repetitive freezing and thawing, now known to induce conformational changes in the molecule and alteration of electrophoretic mobility, results may have been distorted.

**Table II** Creatine kinase isoenzyme distribution in human tissue\*

| Tissue   | CK (IU/Gm)   | MM           | MB       | BB       |
|----------|--------------|--------------|----------|----------|
| Muscle   | 3.00 ± 2.00  | 3.00 ± 2.00  | 0        | 0        |
| Heart    | 1.600 ± 1.60 | 1.370 ± 1.70 | 230 ± 30 | 0        |
| Brain    | 200 ± 30     | 0            | 0        | 200 ± 30 |
| GI tract | 140 ± 20     | 0            | 42 ± 1   | 136 ± 20 |
| Adrenal  | 50 ± 6       | 0            | 0        | 50 ± 6   |
| Lung     | 13 ± 2       | 1 ± 0.2      | 0        | 12 ± 0.5 |
| Kidney   | 9 ± 7        | 1 ± 0.1      | 0        | 8 ± 0.5  |

Data obtained from references 1, 2, 3, 4, 7 and unpublished observations.

Nonspecific fluorescence from moieties other than CK was often not excluded by performing assays both with and without creatine phosphate, the substrate specific for CK. Thus, apparent MB in the skeletal muscle extract may have been an artifact unrelated to any CK isoenzyme. Since electrophoretic scanning techniques are not quantitative, they may have grossly overestimated the amount of MB CK activity present, as was the case in early reports of MB CK content in canine myocardium representing as much as 40 per cent of total CK activity, and therefore twentyfold more than the 2 per cent actually present and measurable with quantitative techniques. However, even a small proportion of MB in skeletal muscle could be associated with release of a significant amount of MB into the circulation after intramuscular injections, muscle trauma, surgery, or shock, potentially clouding the diagnosis of myocardial infarction. Thus, resolution of the question of how much MB is any is present in skeletal muscle was needed.

### Results of quantitative CK isoenzyme assays

The kinetic fluorometric quantitative assay for CK isoenzyme developed in 1974<sup>1</sup> had a sensitivity of 2 IU/L and reproducibility of ± 3 per cent. Human tissues removed at the time of surgery and extracted immediately prior to freezing were assayed with this technique both with and without creatine phosphate to exclude apparent activity from moieties other than CK.<sup>2</sup> As shown in Table II, myocardium was found to contain predominantly MM, with MB representing approximately 15 per cent of total CK activity. Skeletal muscle analyzed included deltoid, pectoralis major and minor, gastrocnemius, and rectus abdominus, all of which contained MM CK.

exclusively Lung, kidney and spleen contained predominantly BB CK with no MB and red blood cells rich in LDH and LDH<sub>1</sub>, an isoenzyme present in myocardium was devoid of appreciable CK activity. Although prostate and the mucosa of the small intestine contained traces of MB (< 3 per cent), myocardium was the only normal human tissue containing appreciable quantities of MB CK. Subsequent development of more rapid and convenient quantitative assays for CK isoenzymes confirmed the impression that human myocardium contains between 15 and 20 per cent MB CK and that skeletal muscle contains only MM.<sup>31, 33</sup>

Since analysis of the CK isoenzyme profile of each skeletal muscle group is not practical, possible heterogeneity of skeletal muscle isoenzyme profiles cannot be excluded easily. Another approach has entailed analysis of plasma CK isoenzymes after spontaneous, surgical, or experimentally induced injury to skeletal muscle. Plasma MB CK is not elevated after intramuscular injections despite utilization of a wide variety of sites for injection and despite marked elevations of total plasma CK.<sup>34, 35</sup> When plasma CK isoenzyme profiles were analyzed at six hour intervals for 24 hours after surgery<sup>36</sup> involving the head and neck, ocular muscles, thorax, abdomen, prostate, urinary bladder or extremities, marked elevations in total plasma CK and MM CK were observed but MB CK remained normal. Analysis of CK isoenzymes by electrophoresis on agarose<sup>37</sup> polyacrylamide gel<sup>38</sup> and cellulose acetate<sup>39</sup> demonstrated the absence of elevation of MB CK after noncardiac surgery, and serial analyses of plasma MB CK with quantitative techniques based on column and batch adsorption chromatography with Sephadex<sup>40, 41</sup> and glycophasic glass beads<sup>42</sup> corroborated the absence of elevated plasma MB CK after surgery.

Among 183 patients undergoing cardiac catheterization<sup>43</sup> total plasma CK was often elevated, but the elevation was due exclusively to MM CK (presumably due to skeletal muscle and soft tissue trauma) in all but two cases. In the two patients with MB CK elevations, transmural myocardial infarction was the cause. In cases of rhabdomyolysis despite total CK elevations of several thousandfold, MB CK remained normal.<sup>44</sup> Elevated total plasma CK after exercise has been attributed to MM CK exclusively. These results of analyses of CK isoenzyme profiles in

human tissues and in plasma after injury to skeletal muscle suggest that elevated plasma MB CK is a virtually specific index of injury to myocardium.<sup>54</sup>

Sensitivity of qualitative electrophoretic techniques for detection of MB CK is of the order of 5 to 10 IU/L.<sup>55, 56</sup> Since plasma from normal subjects contains only 1 to 2 IU/L of MB CK, modest increases in MB CK are not recognized easily with these techniques. Nevertheless, increased activity has been detected consistently in patients with acute myocardial infarction.<sup>1, 2, 11, 44</sup> In contrast, among patients with angina and only transient nonspecific electrocardiographic changes, MB CK did not increase. Operative mortality associated with coronary bypass grafting in 47 patients with unstable angina without elevated plasma MB CK was less than four per cent, similar though slightly greater than mortality associated with this procedure in patients with stable angina but markedly less than mortality (as high as 40 per cent) in patients undergoing surgery during evolving myocardial infarction. Thus, selection of candidates for surgery by exclusion of apparent infarction based on a lack of elevated MB CK avoids the excess mortality associated with surgery in patients with evolving infarction and suggests that absence of elevated MB reflects absence of infarction.<sup>57</sup> Elevated MB CK has been observed in samples from 16 of 111 patients with unstable angina characterized by recurring prolonged episodes of chest pain. However, each of these 16 patients exhibited independent evidence of acute myocardial infarction. MB CK reported in numerous studies of patients with angina without infarction as well as its absence after transient coronary occlusion in experimental animals subjected to ischemia insufficient to produce infarction supports the view that MB CK is released from myocardium only when necrosis occurs.<sup>1, 2, 3, 47, 57</sup> In addition, ischemia alone induced by treadmill exercise and documented electrocardiographically in patients with coronary artery disease<sup>58</sup> does not lead to increased plasma MB CK despite elevated total CK presumably from noncardiac sources.

Depletion of CK from myocardium in experimental animals correlates with morphological criteria of infarction,<sup>41, 46</sup> the magnitude of ST segment elevation,<sup>45</sup> decreased blood flow measured by radioactively labelled microspheres

and alterations in frequency dependent attenuation of ultrasound indicative of infarction<sup>11</sup> Estimates of infarct size based on plasma CK time-activity curves correlate closely with prognosis<sup>1</sup> the severity of angiographically demonstrable wall motion disorders<sup>4</sup> and morphological estimates of infarct size in patients<sup>1</sup> Congestive heart failure uncomplicated by myocardial necrosis and tachycardia are not associated with elevated plasma MB CK even when total CK is increased<sup>1, 6</sup> Thus elevated plasma MB CK reflecting release virtually exclusively from the heart in man appears to differentiate myocardial infarction from coronary insufficiency

MB CK is particularly useful as an index of myocardial infarction occurring in patients after noncardiac surgery<sup>12</sup> Conventionally measured enzymes are elevated and LDH isoenzyme analysis may not be helpful since hemolysis leads to increases in LDH and LDH simulating the isoenzyme pattern resulting after myocardial infarction and present in myocardium itself<sup>13</sup> Mortality<sup>7</sup> associated with infarction after noncardiac surgery is high (sometimes as high as 40 per cent) possibly reflecting delay in initiating appropriate therapy because of delayed recognition of infarction Because postoperative infarction is most common in elderly patients and those with cardiac disease groups in whom definitive electrocardiographic diagnosis is often most difficult differentiation between ischemia and infarction within the first few hours after operation is difficult and may be best achieved by analysis of plasma MB CK activity<sup>5</sup>

On the other hand analysis of plasma MB CK activity after cardiac surgery does not help to establish the presence or absence of intra or perioperative infarction since MB activity is invariably elevated as a result of even minor surgical trauma to the heart<sup>7</sup> Furthermore since the proportion of myocardial MB CK appearing in the circulation may be much greater after surgical trauma than after infarction even quantitative evaluation of MB activity in plasma may not permit differentiation of the two Appearance of Q waves on the electrocardiogram and localized positive findings on myocardial infarct scintigrams with <sup>99m</sup>Tc pyrophosphate appear to be the most useful generally available diagnostic criteria of infarction in this setting<sup>2</sup>

Plasma MB CK appears to remain normal in

patients with pneumonia chronic lung disease and pulmonary emboli even when total plasma CK is increased<sup>14</sup> although elevated MB CK would be anticipated if severe right ventricular failure and ischemia led to right ventricular infarction Pericarditis has not been associated with elevated MB CK<sup>15</sup> but extensive associated epicarditis would be expected to liberate MB CK into the circulation

Increased total CK activity is common in patients with hypothyroidism primarily because of increased MM CK that presumably accumulates due to decreased clearance However on occasion MB CK may be elevated also It has recently been shown that hypothermia is associated with elevated plasma MM but not MB CK presumably because of enzyme release from skeletal muscle<sup>16</sup>

Both MM and MB plasma CK are elevated consistently in patients with muscular dystrophy<sup>17</sup> This appears to result from failure of the normal differentiation or dedifferentiation of skeletal muscle with increasing fetal maturity and hence failure of the normal progression of isoenzyme profiles within the tissue from BB initially to MM and MB at or before term and MM alone by birth or during the neonatal interval<sup>18</sup> In addition MB CK in plasma in patients with muscular dystrophy may reflect release from the dystrophic heart Among patients with polymyositis elevated plasma MB CK though recognized appears to be much less consistent<sup>19</sup>

#### Available MB CK assays

Conventional clinical assays for MB CK generally employ electrophoresis of samples on agarose cellulose acetate or polyacrylamide gels—with visualization procedures capable of detecting 5 to 10 IU/L With these assays myocardial infarction can be detected with a sensitivity and specificity exceeding 95 per cent Sampling at intervals of 6 to 12 hours will usually lead to detection of even small subendocardial infarcts Exclusion of nonspecific fluorescence (and hence false positive results) with control samples run without creatine phosphate as substrate is important particularly since commonly used drugs such as tetracycline aspirin and chlorpromazine can give rise to this phenomenon (Unpublished results)

Quantitative assays offer numerous advantages including comparison of activity in all serial



samples from the same patient in view of their ability to detect some activity in plasma from normal subjects.<sup>47, 51, 5</sup> Since development of a kinetic fluorometric technique in 1974,<sup>47</sup> several sensitive and more rapid quantitative procedures have been implemented. Many utilize Sephadex<sup>47, 51</sup> or cellulose<sup>48</sup> to separate individual CK isoenzymes in a sample by chromatography or batch adsorption. These techniques provide assays more sensitive than those based on electrophoresis and obviate the problem of nonspecific fluorescence. However, incomplete separation and limited sensitivity due to dilution as well as nonspecific binding or denaturation of the enzyme on chromatographic media may pose difficulties.

Recently quantitative assay of MB CK has been accomplished with a radioimmunoassay specific for the B subunit.<sup>49, 50</sup> Lability of enzymatic activity of the antigen during the required radioactive labelling procedure and dissociation of the enzyme into subunits during incubation had precluded previous radioimmunoassay of isoenzymes of CK or other enzymes.<sup>50, 51</sup> The methods developed to overcome these difficulties should be applicable to development of radioimmunoassays for multiple forms of other clinically important isoenzymes as well as for use in an improved quantitative assay for MB CK.

The CK isoenzyme radioimmunoassay<sup>49</sup> detects MB CK reliably with no cross reactivity with MM despite twenty thousandfold molar excess. It is more sensitive than other available assays and capable of detecting as little as 0.01 IU/L of MB CK.<sup>49</sup> Since results are not dependent on enzyme activity but on binding of immunoreactive MB CK protein by the antibody, the assay measures the concentration of enzyme protein. Accordingly, it should be useful in clarifying rates of turnover and denaturation of MB CK and factors influencing clearance of enzymes from the circulation after infarction. Since the radioimmunoassay is so sensitive and since it can detect enzymatically inactive MB CK in the circulation, it is not surprising that it permits detection of infarction earlier than other techniques usually within three hours of the onset of chest pain.<sup>49</sup> Because radioimmunoassay is readily adaptable for automated analysis of large numbers of samples, the MB CK radioimmunoassay should be generally useful for detec-

tion and assessment of severity of myocardial infarction.

### Some advantages of MB CK as a marker of infarction

CK is found in the heart in large quantities and confined virtually exclusively to myocardial cells as opposed to fibroblasts and other components. Since the enzyme is not present in erythrocytes or leukocytes, it is not released from inflammatory exudate in the heart associated with infarction. After myocardial infarction, CK increases in blood within 4 to 6 hours and generally peaks within 12 to 20 hours, permitting rapid diagnosis. The time course of elevation of MB CK is similar but in contrast to total CK, MB CK elevations are virtually specific criteria of myocardial injury. The prompt diagnostic sensitivity and specificity provided by analysis of MB CK activity has important therapeutic as well as economic implications. Since many patients with chest pain are admitted to coronary care units in major medical centers and community hospitals and subjected to sometimes extensive and expensive evaluations, prompt exclusion of infarction is a desirable goal. When serial analyses of MB CK in plasma indicate no elevations of activity for 12 to 24 hours, early transfer of the patient from the intensive care unit can be justified, often permitting more efficient and economical utilization of these specialized facilities and their highly trained contingents of personnel.

### REFERENCES

1. Kontinen A and Sommer H. Determination of serum creatine kinase isoenzymes in myocardial infarction. *Am J Cardiol* 29:817, 1972.
2. Roe CR, Linhard L E, Wagner C S and Nerenberg S T. Combined isoenzyme analysis in the diagnosis of myocardial injury. Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J Lab Clin Med* 80:574, 1972.
3. Roberts R, Gouda K S, Ludbrook J A and Sobel H F. The specificity of elevated serum MB CK activity in the diagnosis of acute myocardial infarction. *Am J Cardiol* 36:433, 1975.
4. Dawson D M and Fine I H. Creatine kinase in human tissues. *Arch Neurol (Chicago)* 15:173, 1977.
5. Rosalki S H. Improved procedure for serum creatine phosphokinase determination. *J Lab Clin Med* 69:676, 1967.
6. Lohmann K. Über die enzymatische aufspaltung der kreatinphosphorsäure zugleich ein beitrag zum mechanismus der muskelkontraktion. *Biochem Z* 271:961, 1934.

- 7 Koedam J C Creatine phosphokinase modified fluorometric method Clin Chim Acta 23 63 1969
- 8 Van der Veen K J and Willebrands A F Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera Clin Chim Acta 13 312 1966
- 9 Morin L G Improved separation of creatine kinase cardiac isoenzyme in serum by batch fractionation Clin Chem 22 97 1976
- 10 Roberts R Sobel B F and Beaslymann B The effect of long term storage on creatine kinase isoenzymes (in preparation 1977)
- 11 Roberts R Henry P D and Sobel B E An improved basis for enzymatic estimation of infarct size Circulation 52 43 19 5
- 12 Sobel B E Markham J and Roberts R Factors influencing enzymatic estimates of infarct size Am J Cardiol 39 130 1977
- 13 Dreyfus J C I S hapira G Resnas J and Scebati L La creatine kinase serique dans le diagnostic du infarctus myocardique Rev Franc Etudes Clin Biol 5 386 1960
- 14 Goldberg D M and Winfield L A Diagnostic accuracy of serum enzyme assays from myocardial infarction in a general hospital population Br Heart J 34 197 19 7
- 15 Smith A F Diagnostic value of serum-creatinase kinase in a coronary care unit Lancet 2 178 1967
- 16 Ebashi H Toyokura Y Momoi H and Sugita H High creatine phosphokinase activity of sera of progressive muscular dystrophy J Biochem (Japan) 46 103 1959
- 17 Hess J W MacDonald R P Frederick R J Jones R N Neely J and Gross D Serum creatine phosphokinase (CPK) activity in disorders of heart and skeletal muscle Ann Intern Med 61 1015 1964
- 18 Matsumoto T Wyte S R Moseley R V Namhauser M M and Henry J N Serum creatinephosphokinase in soft tissue injuries Arch Surg (Chicago) 99 535 1974
- 19 Meltzer H Mrozak S and Boyer M Effects of intramuscular injections of serum creatine phosphokinase activity Am J Med Sci 259 47 1970
- 20 Kotoku T Kawakami H Iwabuchi T Sato T Kutsuzawa T and Nakamura T Clinical significance of serum creatine phosphokinase activity in cerebrovascular diseases Toboku J Exp Med 105 16 19 1
- 21 Lafair J S and Myerson R M Alcoholic myopathy—with special reference to the significance of creatine phosphokinase Arch Intern Med (Chicago) 122 417 1968
- 22 Velez Garcia M Hary P Dioso M and Perloff G T Cysteine stimulated serum creatine phosphokinase Unexpected results, J Lab Clin Med 68 636 1968
- 23 Sobel B F and Shell W M Serum enzyme determinations in the diagnosis and assessment of myocardial infarction Circulation 45 471 1972
- 24 Gutowitz A L Sobel B F and Roberts R Cardiogenic shock A syndrome frequently due to slowly evolving myocardial injury (Abstr) Am J Cardiol 39 322 1977
- 25 Githlis P D Serum enzymes in diseases of the thyroid gland J Clin Pathol 18 660 1965
- 26 Perloff G T Demonstration of creatine phosphokinase in human lung tissue Arch Intern Med (Chicago) 122 3 6 1968
- 27 Henry P D Bloor C M and Sobel B E Increased serum creatine phosphokinase activity in experimental pulmonary embolism Am J Cardiol 26 151 19 0
- 28 King J O and Zapf P A review of the value of creatine phosphokinase estimations in clinical medicine Med J Aust 1 639 1977
- 29 Muggia F M, Ghousein N A and Hanok A Creatine phosphokinase and other serum enzymes during radiotherapy JAMA 211 1345 19 0
- 30 Okada S Sugita H Momoi H Toyokura Y Watanabe T Fba-chi F and Fba-hu S Cysteine stimulated serum creatine kinase in health and disease J Lab Clin Med 84 990 1964
- 31 Dixon C H Jr Fuchs J C A and Fbert P A Changes in serum creatine phosphokinase activity Arch. Surg 103 66 1971
- 32 Meltzer D M Plasma enzymatic activity after exercise Study of psychiatric patients and their relatives Arch. Gen Psychiatry (Chicago) 22 390 1970
- 33 Roberts R and Sobel B E Factors affecting disappearance of creatine phosphokinase (CPK) from the circulation (Abstr) Clin Res 23 205A 1975
- 34 Korsan Bengtson K, Asander L, Blohm G., and Tibblin E Extensive muscle necrosis after long term treatment with aminocaproic acid (EACA) in a case of hereditary periodic edema Acta Med Scand 185 341 1969
- 35 Langer T and Levy R I Acute muscular syndrome associated with administration of clofibrate N Engl J Med 279 856 1968
- 36 Pinder R M Carbenoxolone A review of its pharmacological properties and therapeutic efficacy in peptic ulcer disease Drugs 11 245 1977
- 37 Sueblinvong V and Wilson J F Myocardial damage due to imipramine intoxication J Pediatr 74 475 1979
- 38 Henderson L W Metz M and Wilkinson J H Serum enzyme elevation in glutethimide intoxication Br Med J 3 3 19 0
- 39 West M Gelb D and Zimmerman H J Serum enzymes in disease VII Significance of abnormal serum levels in cardiac failure Am J Med Sci 241 350 1971
- 40 Batsakis J G and Briere R O Interpretive enzymology Springfield Ill Charles C Thomas Publisher
- 41 Kontinen A Huhti V Louhija A and Hartel G Origin of elevated serum enzyme activities after direct current countershock N Engl J Med 281 231 1969
- 42 Michie D D Conley M A Carretta R F and Booth R W Serum enzyme changes following cardiac catheterizations with and without selective coronary arteriography Am J Med Sci 260 11 1970
- 43 Sherwin A L Sifer G R and Elhijali M M Fluorescence technique to demonstrate creatine phosphokinase enzymes Clin. Chim Acta 17 745 1967
- 44 Trauer T D and Gruening D A rapid method for the analysis of creatine phosphokinase isoenzymes Clin Chim Acta 21 151 1968
- 45 Klein M, Shell W E. and Sobel B E Serum creatine phosphokinase (CPK) isoenzymes following intramuscular injections surgery and myocardial infarction Experimental and clinical studies Cardiovasc Res 7 412 1973
- 46 Roberts R and Sobel B E Isoenzymes of creatine phosphokinase and diagnosis of myocardial infarction Ann Intern Med 79 741 1973
- 47 Roberts R Henry P D Witteveen S A G J and Sobel B E Quantification of serum creatine phosphokinase (CPK) isoenzyme activity Am J Cardiol 33 650 1974
- 48 Smith A F Separation of tissue and serum creatine

- kinase isoenzymes on polyacrylamide gel slabs *Clin Chim Acta* 39 351 1972
- 49 Magalhães A S Creatine phosphokinase isoenzymes in human muscle biopsies *Acta Neurol Belg* 70 471 1970
  - 50 Gervin C A Hackel H B and Roe C R Enzyme content of canine cardiac lymph during acute myocardial infarction *Surg Forum* 25 175 1974
  - 51 Henry P D Roberts R and Sobel B E Rapid separation of creatine phosphokinase isoenzymes by batch adsorption with glass beads *Clin Chem* 21 844 1975
  - 52 Mercer D W Separation of tissue and serum creatine kinase isoenzymes by ion exchange column chromatography *Clin Chem* 20 36 1974
  - 53 Yasmuneh W G and Hanson N Q Electrophoresis on cellulose acetate and chromatography on DEAE Sephadex A 50 compared in the estimation of creatine kinase isoenzymes *Clin Chem* 21 381 1975
  - 54 Roberts R and Sobel B E Elevated plasma MB creatine phosphokinase activity A specific marker for myocardial infarction in perioperative patients *Arch Intern Med* 136 421 1976
  - 55 Dixon S H Lumbird L E and Roe C R Recognition of post operative acute myocardial infarction Application of isoenzyme techniques *Circulation* 48(Suppl III) III 137 1973
  - 56 Smith A F Radford D Wong C P and Oliver M F Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction *Br Heart J* 38 225 1976
  - 57 Roberts R Sobel B E and Ludbrook P A Determination of the origin of elevated plasma CPK after cardiac catheterization *Cath Cardiovasc Diag* 2 329 1976
  - 58 Roberts R and Sobel B E CPK enzymes in evaluation of myocardial ischemic injury *Hosp Prac* 11 55 1976
  - 59 Klein M S Ludbrook P A Mims J W Gafford F H Gillespie T A Weldon C S Sobel B E and Roberts R Perioperative mortality rate in patients with unstable angina selected by exclusion of myocardial infarction *J Thorac Cardiovasc Surg* 73 253 1977
  - 60 Klein M S Coleman R E Roberts R and Weiss A N <sup>99m</sup>Tc(Sn) Pyrophosphate scintigrams in exercise induced angina and calcified valves *Am J Cardiol* 37 149 1976
  - 61 Kjekshus J K and Sobel B E Depressed myocardial creatine phosphokinase activity following experimental myocardial infarction in rabbit *Circ Res* 27 403 1970
  - 62 Shell W E Kjekshus J K and Sobel B E Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase (CPK) activity *J Clin Invest* 50 2614 1971
  - 63 Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusion *Circulation* 43 67 1971
  - 64 Mims J W Yuhas D E Miller J G Weiss A N and Sobel B E Detection of myocardial infarction in vitro based on altered attenuation of ultrasound *Circ Res* 41 192 1977
  - 65 Sobel B E Bresnahan J F Shell W F and Yoder R D Estimation of infarct size in man and its relation to prognosis *Circulation* 46 640 1972
  - 66 Rogers W J McDaniel H G Smith L R Mantle J A Russell R O Jr and Rackley C E Correlation of CPK MB and angiographic estimates of infarct size in man (Abstr) *Circulation* 54(Suppl II) II 28 1976
  - 67 Bleifeld W Matheis D Hanrath P Buss H and Effert S Infarct size estimated from serial serum creatine phosphokinase in relation to left ventricular hemodynamics *Circulation* 55 303 1977
  - 68 Rabinowitz H Clejan S and Neufeld H N CPK isoenzymes in supraventricular tachyarrhythmias *Am J Cardiol* 35 164 1975
  - 69 Lauria J I King H D and Markello R Transaminase values following anesthesia and surgery *N Y J Med* 69 2003 1969
  - 70 Watkins S M and Lewis A Serum enzyme levels in diagnosis of postoperative myocardial infarction *Br Med J* 3 733 1972
  - 71 Dawson J T Hall R J Hollman G L and Cooley D A Mortality in patients undergoing coronary artery bypass surgery after myocardial infarction *Am J Cardiol* 33 483 1974
  - 72 Klein M S Coleman R E Weldon C S Sobel B E and Roberts R Concordance of electrocardiographic and scintigraphic criteria of myocardial injury after cardiac surgery *J Thorac Cardiovasc Surg* 71 934 1976
  - 73 Fleg J L Siegel B A and Roberts R Detection of pericarditis with <sup>99m</sup>Technetium pyrophosphate images (Abstr) *Am J Cardiol* 39 273 1977
  - 74 Karlsberg R P Siegel B A and Roberts R Effect of altered thyroid function on the disappearance of creatine kinase (Abstr) *Clin Res* 25 297A 1977
  - 75 Maclean D Griffiths P D and Emble Smith D Serum enzymes in relation to electrocardiographic changes in accidental hypothermia *Lancet* 2 1966 1968
  - 76 Kar N C and Pearson C M Creatine phosphokinase isoenzymes in muscle in human myopathies *Am J Clin Pathol* 43 207 1965
  - 77 Eppenberger H M Eppenberger M Richterich R and Aepli H The ontogeny of creatine kinase isoenzymes *Develop Biol* 10 1, 1964
  - 78 Galen R S Reiffel J R and Gambino S R Diagnosis of acute myocardial infarction *JAMA* 232 145 1975
  - 79 Roberts R Parker C W Sobel B E and Painter A A Radioimmunoassay of MB (myocardial) CPK (Abstr) *Clin Res* 24 238A 1976
  - 80 Roberts R Sobel B E and Parker C W Radioimmunoassay for creatine kinase isoenzymes *Science* 194 835 1976
  - 81 Roberts R Parker C W Sobel B E and Painter A A Radioimmunoassay of human MB CK (Abstr) *Circulation* 54(Suppl II) II 152 1976
  - 82 Painter A Sobel B E and Roberts R Prompt detection of myocardial infarction by radioimmunoassay of MB creatine kinase (Abstr) *Am J Cardiol* 39 317 1977

# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

## Management of shock following acute myocardial infarction Part I Drug therapy

Leslie A. Kuhn M.D.  
New York, N.Y.

About 10 years have elapsed since we evaluated the nature and treatment of cardiogenic shock in this section. These years have seen some advance in elucidating the hemodynamic patterns of the shock state and in the use of a variety of therapies. Regrettably, however, the mortality rate has remained quite high. We will analyze the effects of medical therapy in Part I and the use of therapeutic mechanical circulatory assistance in Part II of these articles.

### Hemodynamic subsets in acute myocardial infarction

Increased use of relatively simple bedside methods to assess alterations of cardiac output by means of thermodilution techniques and left ventricular function with the aid of a Swan Ganz catheter to measure pulmonary wedge or pulmonary artery diastolic pressure (reasonably accurate gauges of left ventricular end diastolic or filling pressure) has led to more precise knowledge of hemodynamic alterations which occur following acute myocardial infarction and the effects of therapeutic interventions. In addition, this has permitted some correlation between hemodynamic alterations and a variety of clinical manifestations. In the shock state characterized by widespread circulatory insufficiency there is almost invariably a profound reduction of cardiac index generally to below  $1.8 \text{ L/min/M}^2$ . Clinical degrees of hypoperfusion usually demonstrate

cardiac indices of  $1.8$  to  $2.2 \text{ L/min/M}^2$ . With clinical evidence of pulmonary congestion generally the wedge pressure (or its equivalents) will exceed  $18 \text{ mm Hg}$ . There are, however, significant exceptions to these generalizations which render precise clinical hemodynamic correlations somewhat inexact. A substantial number of patients (perhaps as many as 25 per cent) without clinical suggestion of underperfusion can have appreciable reduction of cardiac index below  $2.2 \text{ L/min/M}^2$ . Similarly, about 15 per cent of patients without clinical evidence of pulmonary congestion will demonstrate wedge pressures exceeding  $18 \text{ mm Hg}$ . One common pitfall is to obtain hemodynamic measurements after urgent diuretic therapy has been administered. Although rales and roentgenographic evidence of pulmonary congestion may be present, there may have been rapid reduction of pulmonary wedge pressure to normal levels. In chronic pulmonary disease of course rales may be present with normal cardiac output and wedge pressure. In addition, in some patients with chronic congestive heart failure it may be difficult to distinguish acute hemodynamic change due to the infarction from longstanding hemodynamic alterations. Generally, however, mortality will be substantially higher in patients with wedge pressures greater than  $18 \text{ mm Hg}$  and cardiac indices below  $2.2 \text{ L/min/M}^2$ .

On the basis of these criteria, clinical and hemodynamic subsets have been defined and correlated with mortality. Thus, a normal clinical and hemodynamic setting is associated with a 1 to 3 per cent mortality rate, whereas clinical and hemodynamic pulmonary congestion and hypoperfusion are associated with a 51 to 60 per cent

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, N.Y.  
Received for publication December 15, 1977.  
Reprint requests: Leslie A. Kuhn, M.D., Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, N.Y. 10029.



# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

## Management of shock following acute myocardial infarction Part I Drug therapy

Leslie A. Kuhn M.D.  
New York, N.Y.

About 10 years have elapsed since we evaluated the nature and treatment of cardiogenic shock in this section. These years have seen some advance in elucidating the hemodynamic patterns of the shock state and in the use of a variety of therapies. Regrettably, however, the mortality rate has remained quite high. We will analyze the effects of medical therapy in Part I and the use of therapeutic mechanical circulatory assistance in Part II of these articles.

### Hemodynamic subsets in acute myocardial infarction

Increased use of relatively simple bedside methods to assess alterations of cardiac output by means of thermodilution techniques and left ventricular function with the aid of a Swan Ganz catheter to measure pulmonary wedge or pulmonary artery diastolic pressure (reasonably accurate gauges of left ventricular end diastolic or filling pressure) has led to more precise knowledge of hemodynamic alterations which occur following acute myocardial infarction and the effects of therapeutic interventions. In addition, this has permitted some correlation between hemodynamic alterations and a variety of clinical manifestations. In the shock state characterized by widespread circulatory insufficiency, there is almost invariably a profound reduction of cardiac index generally to below  $1.8 \text{ L/min/M}^2$ . Clinical degrees of hypoperfusion usually demonstrate

cardiac indices of 1.8 to  $2.2 \text{ L/min/M}^2$ . With clinical evidence of pulmonary congestion generally the wedge pressure (or its equivalents) will exceed 18 mm Hg. There are, however, significant exceptions to these generalizations which render precise clinical hemodynamic correlations somewhat inexact. A substantial number of patients (perhaps as many as 25 per cent) without clinical suggestion of underperfusion can have appreciable reduction of cardiac index below  $2.2 \text{ L/min/M}^2$ . Similarly, about 15 per cent of patients without clinical evidence of pulmonary congestion will demonstrate wedge pressures exceeding 18 mm Hg. One common pitfall is to obtain hemodynamic measurements after urgent diuretic therapy has been administered. Although râles and roentgenographic evidence of pulmonary congestion may be present, there may have been rapid reduction of pulmonary wedge pressure to normal levels. In chronic pulmonary disease, of course, râles may be present with normal cardiac output and wedge pressure. In addition, in some patients with chronic congestive heart failure, it may be difficult to distinguish acute hemodynamic change due to the infarction from longstanding hemodynamic alterations. Generally, however, mortality will be substantially higher in patients with wedge pressures greater than 18 mm Hg and cardiac indices below  $2.2 \text{ L/min/M}^2$ .

On the basis of these criteria, clinical and hemodynamic subsets have been defined and correlated with mortality. Thus, a normal clinical and hemodynamic setting is associated with a 1 to 3 per cent mortality rate, whereas clinical and hemodynamic pulmonary congestion and hypoperfusion are associated with 51 to 60 per cent

From the Division of Cardiology Department of Medicine Mount Sinai School of Medicine, New York, N.Y.

Received for publication Dec 15, 1977

Reprint request: Leslie A. Kuhn, M.D., Division of Cardiology, Dept. of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th St., New York, N.Y. 10029

mortality rate. The shock state, characterized by hypoperfusion and profound hypotension can be considered a further subdivision of this latter group and generally has been associated with a still higher mortality rate, in most instances about 85 to 90 per cent.

### Vasopressors

The rationale for the use of vasopressor therapy in acute myocardial infarction with shock is based on physiological considerations as well as clinical experience. Animal experiments and human studies have shown that the function of the ischemic ventricle is dependent on adequate coronary flow. The principal controlling influence on coronary flow is adequate coronary perfusion pressure. In a clinical setting this is generally a minimum of 80 to 90 mm Hg systolic pressure. Patients in clinical shock following acute myocardial infarction will survive only rarely unless arterial pressures of at least this level are attained because continued arterial hypotension results in further deterioration of ventricular function with resultant further hypotension and circulatory insufficiency, acidosis, and usually an irreversible clinical state. In addition, because of continuing hypotension and its attendant myocardial ischemia, there is increased susceptibility to life threatening ventricular arrhythmias. Therefore it is advisable to raise arterial pressure to about 90 to 100 mm Hg systolic as rapidly as possible. A pressor agent such as norepinephrine (which also has some inotropic or beta mimetic effect) generally achieves this promptly. Of course with the rise of arterial pressure from shock levels to more normal levels there is an accompanying increment in myocardial oxygen requirement but the increase in coronary flow associated with the rise of arterial pressure results in improvement of cardiac output and usually improvement of myocardial metabolism to an aerobic from an anaerobic mode as measured by alteration of lactate production. Therefore the net effect of norepinephrine when used in a setting with abnormally low arterial pressure in acute myocardial infarction is beneficial hemodynamically and metabolically. Although mortality has remained very high in the shock syndrome with use of norepinephrine the survivors generally demonstrate an adequate arterial pressure rise. Norepinephrine remains a useful agent because

its effects are prompt and it is the most potent pressor available. It may afford time to assess the hemodynamic and clinical situations to determine what additional modalities of treatment are necessary.

Dopamine and metaraminol are also useful for the same reasons but neither is quite as prompt in its action or as potent as norepinephrine. Dopamine which acts to preserve or enhance renal arterial flow in contrast to norepinephrine, is particularly useful in long-standing shock when there is substantial reduction of renal function or in patients with preexisting renal dysfunction. Metaraminol can be given by the intramuscular route or by intravenous injection undiluted and does not cause sloughing of the skin if it infiltrates through the vein. It has some advantage because of this in certain clinical settings where it is not feasible to prepare a diluted intravenous infusion necessary for norepinephrine administration. However, it is not as potent as norepinephrine and since it is thought to depend on tissue norepinephrine for its efficacy, it may lose effectiveness during prolonged use. In such instances norepinephrine may give the desired pressor effect.

### Inotropic agents

Inotropic agents with strong beta mimetic properties, such as isoproterenol have achieved some success when used in hypotension following cardiac surgery and in clinical states other than acute myocardial infarction. In acute myocardial infarction with shock both clinical and experimental investigations have indicated little efficacy of this agent and some hazard. Because of its inotropic effects in increasing the rate of rise of left ventricular pressure, oxygen requirement of the left ventricle is increased. Since it generally fails to cause an increment in coronary perfusion pressure and flow the net effect results in persistence or increase of anaerobic ventricular metabolism and accompanying undesirable chronotropic effects. However when used in a setting in which adequate arterial pressure is maintained with a pressor agent or with mechanical circulatory support beneficial hemodynamic and cardiac metabolic effects may be achieved.

The use of digitals in acute myocardial infarction has been controversial. When used in normal dogs myocardial infarct size has been increased. However experimental and clinical studies in

infarction with heart failure or shock have shown improvement towards normal of cardiac output, left ventricular end diastolic pressure and myocardial metabolism. The hazards due to its use are probably of minor consequence and generally controllable when the drug is used with appropriate caution. Usually it is administered in somewhat lower dosage than in other situations, starting with one half the digitalizing dose. While favorable hemodynamic effects are achieved, they rarely are sufficient by themselves to adequately reverse the shock state.

A newer synthetic catecholamine, dobutamine, has been used in end stage congestive heart failure due to cardiomyopathy with beneficial changes in hemodynamic performance as measured echocardiographically. The use of the agent in acute myocardial infarction with shock has been too sparse to form an opinion as to its efficacy at this time.

#### Miscellaneous agents

Other agents such as high dose steroids, glucose-insulin-potassium infusion and glucagon have been used with varying results, particularly in experimental myocardial infarction. Their efficacy and hazards in clinical acute myocardial infarction with shock have not been established sufficiently to warrant using them on other than an experimental basis at present. Limitation of space does not permit full discussion of experiments concerning their use.

#### Volume expansion

The patient with acute myocardial infarction and shock is underperfused and in those without obvious clinical congestive heart failure may often give the appearance of blood volume deficit. However, measurements in such patients have failed to indicate significant reductions of blood volume as a fraction of predicted normal values in comparison with patients with infarction without shock, patients in the recuperative stages of myocardial infarction or in normal patients. There are clinical situations in which fluid loss is obvious in the hypotensive patient such as post operative hemorrhage, profound diuresis or diaphoresis or vomiting or possibly with peripheral pooling subsequent to heavy narcotic administration. Generally this background is not present in the patient with acute myocardial infarction with shock and it must be determined

whether fluid administration is indicated or might be harmful. The most precise method of determining this is by measurement of pulmonary wedge pressure and the Swan Ganz catheter has been most valuable for this purpose. If this technique is not available, clinical assessment must be made and this may at times be adequate but at other times it may lead to serious error. Use of right sided events such as central venous pressure measurement or clinical approximation of venous pressure by examination of the neck veins may give an erroneous view of left sided dynamics in acute myocardial infarction. The function curves of the right and left ventricles differ particularly when there is predominantly left sided dysfunction as in the great majority of cases of acute myocardial infarction. The right sided pressure may be normal (with normal central venous pressure) in the presence of markedly elevated left sided pressure. With fluid administration in acute myocardial infarction the right sided pressure may rise only slightly but there may be great rises of left ventricular end-diastolic pressure to pulmonary edema levels. Therefore if the neck veins are flat and central venous pressure is normal it should be appreciated that fluid administration may still be hazardous in acute myocardial infarction. If central venous pressure is above normal the left sided pressure will almost always be elevated also and generally fluid administration should be avoided. One exception to this is in right ventricular infarction (which simulates inferior infarction electrocardiographically) in which instance the right sided pressure may be elevated and the left sided pressure normal. Although this is uncommon (but perhaps more frequent than previously thought according to recent studies with radionuclide scans) fluid administration is important in restoring the depressed cardiac output and arterial pressure to normal in such patients.

Traditional clinical signs of heart failure may also be misleading as pulmonary rales and dyspnea do not correlate consistently with elevated pulmonary wedge pressure. Appearance of pulmonary congestion on the chest x ray may also show lack of correlation with wedge pressure because of phase lag. There may be normal or even low wedge pressures when the x ray picture of congestion has not cleared and there may be elevated wedge pressures in



the absence of confirmatory chest x ray changes. A third heart sound is probably the best clinical estimate of an elevated 'wedge' pressure, but this is not uniformly reliable."

Blood volume expansion with glucose in water, dextran or serum albumin has been reported efficacious in elevating arterial pressure and cardiac output in some patients with acute myocardial infarction and shock. The number of patients responding to such treatment has varied considerably in different reports, probably owing to different definitions of shock. In some, as many as 20 per cent of patients with shock are reported to be benefited by fluid administration. In our own experience this therapy only very rarely relieves the shock state unless there is obvious fluid or blood loss or the patient is in the early postoperative state. Some of the measurements of normal or low 'wedge' pressures have been obtained after diuretic administration. In some reports and in our own experience, patients with acute myocardial infarction and shock, before treatment will almost invariably demonstrate high wedge pressures generally above 15 to 18 mm Hg reflecting the profound degree of left ventricular damage known to exist in shock patients.

Careful studies of ventricular function in acute myocardial infarction have demonstrated some increment of cardiac output with elevation of left ventricular filling pressure (assessed by wedge pressure in most instances) to levels of about 20 to 24 mm Hg.<sup>11</sup> Beyond this point, the function curve begins to flatten and further increments of pressure do not result in increased cardiac output, but pulmonary edema may be produced. Therefore if the 'wedge' pressure is low, cautious attempts to raise the pressure to levels of about 20 mm Hg may be made. However since the ability of the infarcted ventricle to eject a volume load without a sharp pressure increment may be seriously impaired because of poor compliance, a relatively mild increment of volume may result in a marked rise of filling pressure and clinical signs of congestive heart failure. From these considerations, it is prudent to monitor wedge pressure carefully when administering volume expanding agents. In our experience if hemodynamic improvement is obtained with these measures it is usually temporary unless there is an obvious fluid deficit. Volume expansion is not used if the 'wedge' pressure is elevated if the patient has an

S<sub>3</sub> or obvious clinical congestive heart failure with rales that have appeared under observation orthopnea and tachypnea.

### Diuretics

Diuretics, particularly rapidly acting intravenously administered furosemide or ethacrynic acid, remain the most important agents for symptomatic relief of congestive heart failure and for prompt, predictable lowering of elevated left ventricular diastolic pressure whether or not shock is present. They usually produce little rise of cardiac output, but a small reduction of ventricular volume can result in a substantial fall of ventricular diastolic pressure. Despite small alteration of cardiac output the patient generally improves substantially symptomatically and there may be prompt relief of tachypnea and orthopnea with their attendant apprehension and tachycardia. It is probable that susceptibility to life threatening arrhythmias is diminished by reduction of elevated ventricular volume and ventricular diastolic pressure. Therefore the prompt administration of these agents when congestive heart failure is present is important and is usually beneficial.

### Vasodilators

There has been a rapidly growing literature concerning the use of a variety of vasodilators in congestive heart failure with and without acute myocardial infarction. In general, cardiac output has risen moderately and elevated wedge pressure has shown a somewhat more marked decline. Different drugs classified as vasodilators may have differing actions. Nitroglycerin and the long acting nitrates act primarily to reduce preload, hydralazine to reduce impedance and afterload and nitroprusside has dual effects. There is some evidence that nitroglycerin and nitroprusside may have different effects on the coronary circulation, nitroglycerin enhancing flow to ischemic areas and nitroprusside failing to do this, producing increased ischemia.<sup>12</sup> When the wedge pressure is normal or reduced vasodilators may cause a further fall of an already depressed cardiac output.<sup>13</sup> In addition nitroprusside infusion has been associated with a reduction of arterial oxygen pressure probably due to increased perfusion of underventilated portions of the lungs.<sup>14</sup>

Despite the favorable hemodynamic altera-

tions produced by these agents in congestive heart failure their precise role in the treatment of acute myocardial infarction has not been fully delineated. They are most rational when the arterial pressure is substantially elevated and there is recurrent ischemic pain and congestive heart failure particularly in association with significant mitral regurgitation where reduction of peripheral vascular resistance causes reduction of the regurgitant fraction and enhanced forward flow. In normotensive patients with congestive heart failure while there may be measurable hemodynamic improvement with the vasodilators the patient may usually be managed with conventional diuretics and digitalis. In severe heart failure the vasodilators may be useful but rarely are sufficiently efficacious by themselves.

In the patient with acute myocardial infarction with shock there have been some reports of successful use of vasodilators with reduction of early mortality to about 50 per cent (with disappointing results for post hospitalization salvage).<sup>1</sup> However favorable results in shock have not been attained consistently and there are considerable hazards to their use. This difference in reported survival with the use of these and other agents in cardiogenic shock probably results from different definitions of the shock syndrome. When marked arterial pressure reduction to below 80 to 90 mm Hg systolic is an integral part of the definition results of therapeutic interventions are almost uniformly more pessimistic than when the syndrome is more loosely defined by reduction of cardiac output or reduction of arterial pressure to a percentage of what it was in the preinfarction state. In such instances the natural course of the disease and its treatment with conventional agents are more favorable as there is probably less profound myocardial damage. There are no adequate randomized studies in different groups of patients using the therapeutic agents advocated for the treatment of shock following acute myocardial infarction.

A priori it would appear undesirable to use an agent which can further depress an already critically low arterial pressure. While the vasodilators can often achieve reduction of ventricular diastolic pressure and elevation of cardiac output without a significant fall of arterial pressure their actions at other times are unpredictable and substantial falls of arterial pressure may result from relatively small doses. Generally at low

doses this will not occur and reduction of cardiac output and arterial pressure are more commonly seen at medium to high dose levels but we have observed several instances of profound arterial pressure reduction with low doses of nitroprusside or nitrates. Hemodynamic monitoring of wedge and arterial pressures is of prime importance when these agents are used particularly when the patient is hypotensive and care must be taken not to allow significant reduction of the already depressed arterial pressure. The impact of vasodilators in the shock state is probably minor in regard to patient survival but it is probable they may be useful adjuvants when used with other modalities which can maintain arterial pressure such as the intra aortic balloon or pressor agents.

### Conclusions

Shock following acute myocardial infarction when defined reasonably rigidly to include arterial systolic hypotension of below 80 to 90 mm Hg in association with signs of underperfusion continues to cause very high mortality despite all attempts at therapy. Vasopressor agents are generally effective in promptly restoring arterial pressure towards normal. Subsequent treatment relies on clinical observations and hemodynamic measurements. Diuretics are helpful in promptly reverting pulmonary congestion. Digitalis may be used as an adjuvant agent. Other inotropic drugs such as isoproterenol generally are ineffective and may be hazardous when used in a hypotensive patient with acute myocardial infarction. Blood volume expansion is helpful in the patient with reduction of cardiac output and low ventricular filling pressure an unusual circumstance in shock following myocardial infarction unless there has been obvious fluid loss. The benefits of vasodilator agents have not been fully established in the shock state and they may be hazardous sometimes unpredictably causing further depression of an already low arterial pressure.

Although drug therapy can be more intelligently managed with the aid of appropriate hemodynamic measurements and there are some survivors attributable to pharmacologic agents the great majority of patients are not ultimately successfully treated. This is because there is profound myocardial damage once shock has developed and in many instances it is irreversible.

For significant improvement in mortality rate attention must be directed toward prevention of the shock state by vigorous management of lesser degrees of heart failure, early hypoperfusion and significant arrhythmias, all of which may culminate in shock.

## REFERENCES

- Forrester J E, Diamond G, Chatterjee K and Swan H J C Medical therapy of acute myocardial infarction by application of hemodynamic subsets *N Engl J Med* 295 1356 1404 1976
- Gunnar R M, Loeb H A, Pietras R D and Tobin J B Jr Ineffectiveness of isoproterenol in shock due to acute myocardial infarction *J A M A* 202 1124 1967
- Kuhn L A, Kline H J, Marano A J, Cohn L J, Weinrauch H and Berger M Hemodynamic and cardiac metabolic effects of mechanical increase of vascular resistance in experimental myocardial infarction with shock *Circ Res* 19 1086 1966
- Mueller H, Ayres S M, Giannelis S Jr et al Effects of isoproterenol, 1 norepinephrine and intraaortic counterpulsation on hemodynamics and myocardial metabolism in shock following acute myocardial infarction *Circulation* 45 335 1972
- Kuhn L A, Kline H J, Goodman P and Johnson C D Effects of isoproterenol on hemodynamic alterations, myocardial metabolism and coronary flow in acute myocardial infarction with shock *Am Heart J* 77 772 1969
- Marano A J, Kline H J, Kuhn L A and Cestero J The hemodynamic effects of ouabain in experimental acute myocardial infarction with shock *Am J Cardiol* 17 327 1966
- Rahimtoola S H, Sinno M Z, Chuquimia R et al Effects of ouabain on impaired left ventricular function in acute myocardial infarction *N Engl J Med* 287 59, 1972
- Bush C A, Weibel J and Leiter C V Treatment of end stage cardiac failure with dobutamine (Abstr) *Am J Cardiol* 37 125 1976
- Smith W W, Wikler N E and Fox A C Hemodynamic studies of patients with myocardial infarction *Circulation* 9 352 1954
- Kupfer S Can experimental shock be induced by coronary occlusion? *Proc Soc Exp Biol Med* 76 134 1951
- Ratshun R A, Rackley C E and Russell R O Jr Hemodynamic evaluation of left ventricular function in shock complicating myocardial infarction *Circulation* 45 127 1972
- Rackley C E and Russell R O Jr Left ventricular function in acute myocardial infarction and its clinical significance *Circulation* 45 231 1972
- Engler H L, Pearlman H S, Goldstein R A, Kent K M and Epstein S E Relative effects of nitroglycerine and nitroglucine on ischemia after experimental coronary occlusion *Clin Res* 24 216A 1976
- Gold H A, Leimbach R C and Sanders C A Use of sublingual nitroglycerine in congestive failure following acute myocardial infarction *Circulation* 46 839 1972
- Mookherjee S, Keighley F H Jr, Warner R A, Bowser M A and Obeid A I Hemodynamic ventricular and blood gas changes during infusion of sodium nitroferriyanide (Nitroprusside) Studies in patients with congestive heart failure *Chest* 72 273 1977
- Chatterjee K, Swan H J C, Kaushik V S, Sobin G, Magnusson P and Forrester J S Effects of vasodilator therapy for severe pump failure in acute myocardial infarction on short term and late prognosis *Circulation* 53 797 1976
- Smith H J, Goldstein R A, Kent K M, Aamodt R and Epstein S E Reduction of ischemia by nitroglycerine and methoxamine Mechanism of action (Abstr) *Am J Cardiol* 37 174 1976

## Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. P.O. Box 765, Schenectady, N.Y. 12301 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

## Of teaching hygiene

Several decades ago hygiene was a mandatory part of the elementary and high school curricula for all children of America. Children were taught to wash their hands as well as why how and when to do so. They were taught the proper care of teeth and oral hygiene. They learned to use soap and water and the need for bathing regularly. They learned about diseases and infections: contagious illnesses and nutritional illnesses. They learned about germs: bacterial and viral and they learned where these agents resided in great abundance: how they infected man, their portal of entry, the diseases they produced and the methods of their dissemination. Children were taught the fundamentals of nutrition: play, rest, sleep, happiness, obedience and discipline. They learned of the respective roles of their parents, teachers and fellow students. The importance of early care of illnesses, the need of adequate lighting to read and study and the value of fresh clean air were all discussed in the classroom. The students learned about toxic agents and how to avoid them. Their hands and fingernails were inspected daily by the teachers. The children were advised to keep their hands clean, their nails trimmed and their clothes clean and neat regardless of the cost or quality of the clothing. Students learned to be proud and loyal to America, how to play together, win or lose. These and many other important instructions for mental and physical health and for happiness were taught regularly each year. Good physical and mental health and happiness of the students were the concerns of the teachers. Students learned the proper sense of values for good mental health as well as for good physical health.

But today there is little or no hygiene taught. Habit forming drugs are known to be used in high schools and even in elementary schools at present. Permissiveness and sexual behavior are the concerns of today.

One merely has to observe people entering and leaving public restrooms to see how inappropriately they wash their hands if they wash them at all. People cough and sneeze into the faces of others and blow their nasty tobacco smoke into the faces of those about them.

Few children have seen a bacterium, protozoan or virus under a microscope or have learned anything concerning their characteristic features.

Why are there no more classes in hygiene? Why not teach the hazards of insecticidal sprays, Lysol spray, deodorant sprays, hair sprays, and other agents and practices that are so toxic and that are polluting the American home? It is well known that preventive medicine is more important than curative medicine. There is no doubt about that. So shouldn't hygiene be a part of all elementary and high school curricula and be taught by knowledgeable teachers?

G E Burch M.D.  
Tulane University School of Medicine  
and Charity Hospital of Louisiana  
New Orleans, La

### REFERENCE

1. Burch G E. Toxic agents, cardiovascular disease and the polluted home. *Am Heart J* 87:619, 1974.

## The problem of cell aggregation during coronary artery bypass procedures

The mechanical transfer of blood during cardiac bypass procedures has often been complicated by the problem of particle aggregate formation and the need to remove these aggregates through filtering. It is common practice to attempt to control this difficulty through the use of heparin, the rationale being that the anticoagulant properties of heparin will serve to disperse particles and keep aggregation from occurring. Experience to date, however, indicates that heparin, even in high concentrations, often fails to prevent or reverse the process of aggregation.

To the best of our knowledge, no satisfactory proposal presently exists to account for particle formation under these conditions in the lines of the pump and presumably in the blood stream of the patient, nor has a rationale of prophylaxis

been available to prevent this potentially adverse development.

In our laboratory, *in vitro* experiments have demonstrated that when a drug such as heparin is added in increasing doses to whole blood, a concentration-dependent biphasic reaction results. Both microscopic and sedimentation rate studies indicated that with low concentrations of heparin, dispersion of red blood cells occurs. This phenomena constitutes the first phase. However, with addition of increasing concentrations of heparin, these cells were observed to aggregate. Replication of this experiment using a different molecule for each experiment, i.e. coumadin, albumin, mucopolysaccharides, etc., yielded the same biphasic pattern of dispersal followed by aggregation.

It is our proposal that the observed reaction of dispersal followed by aggregation is a function of the surface active properties of the heparin coumadin etc molecules acting on the surfaces of cells and the surfaces of other particles present in the blood. Heparin or other surfactant molecules accumulating at the cell surfaces form films. adjacent films then adhere to each other causing aggregation to occur. Albumin and fragments of cells are also capable of layering out on surfaces to form films and in a manner similar to that evoked by high concentrations of heparin to produce aggregation. The point to be emphasized is that to prevent particle aggregation an optimal concentration of the anticoagulating or antiaggregating agent must be present in the circulating blood during the bypass procedures. Optimal is used to mean

that concentration of drug at which dispersion has fully occurred and beyond which aggregation will be initiated. This concentration can be quickly and empirically determined through microscopic examination of blood samples which are routinely drawn during bypass surgery.

Bernard Ecanou Ph.D.  
Bernard H. Gold Ph.D.  
University of Illinois  
at the Medical Center  
Chicago Ill.  
Max Sadove M.D.  
Rush Medical Center  
Chicago Ill.

## To each according to his desert

Bed rest is one measure which is generally used in the management of a patient with acute myocardial infarction. The length of bed rest of such patients varied a great deal with the passage of time. According to Lewis, rest in bed should be continued for at least eight weeks even in the milder cases to ensure firm cicatrization of the ventricular wall. A number of patients have lost their lives and especially those who have early recovered from symptoms by neglect of these precautions. Most authors recommended a bed rest of six weeks duration. This is a far cry from the few days of bed rest advocated lately. The long bed rest in general use was influenced by a few experimental studies performed by pathologists.

As early as 1916 Karsner and Dwyer<sup>1</sup> had found necrotic tissue in the myocardium 60 days after ligation of a coronary artery in dogs. More than two decades later Mallory White and Saledo Salazar<sup>2</sup> in their classical paper showed that it took five weeks for the removal of necrotic material after an infarction. While small infarctions in dogs healed in about five weeks, large ones healed completely in two months. Therefore to every clinician the long bed rest for patients with acute myocardial infarction seemed to be absolutely necessary. This viewpoint found support in a study which revealed a higher incidence of rupture of the myocardium in mental patients with acute myocardial infarction who were ambulatory. 73 per cent of patients with an acute myocardial infarction died from cardiac rupture and tamponade. Furthermore experiments on dogs showed that after ligation of the ramus descendens anterior rest led to healing of the infarction with production of a small firm scar without thinning of the ventricular wall while early exercise (within three days after the operation) resulted in thin scars with aneurysmal bulging.

The often quoted experiments by Thomas and Harrison are not pertinent because the myocardium was only slightly damaged by burning; the authors themselves caution not to draw conclusions concerning patients.

For many years now perhaps influenced by statements pointing out the harm done by prolonged bed rest, patients

with acute myocardial infarction were asked to be out of bed early and were discharged early from the hospital. Already in 1959 Brummer and colleagues questioned the need for long bed rest in the management of acute myocardial infarction. Groden and associates<sup>3</sup> did not find any significant difference in mortality rate, development of hypotension, shock or heart failure, further episodes of chest pain, incidence of arrhythmias in two groups of patients with acute myocardial infarction when mobilized early or late and discharged from the hospital early or late. The authors also state that there was no difference in the long term incidence of ventricular aneurysms in the two groups. One of their groups stayed in the hospital three weeks and the other five weeks.

In addition to venous thrombosis and pulmonary embolism, muscular atrophy, economic and psychologic effects were mentioned as arguments against prolonged bed rest, thus completely disregarding the findings of pathologists mentioned above. It is also significant with today's reliance on instrumental findings that in more recent studies the presence or absence of gallop rhythm, distant muffled heart sounds, rales over the bases of the lungs, often even the level of blood pressure, are not considered in a decision of the duration of bed rest.

In numerous recent studies more authors tried to demonstrate that still earlier ambulation and earlier discharge from the hospital did not increase mortality and morbidity and did not lead to the formation of a cardiac aneurysm. Some authors discharge patients with acute myocardial infarction even after 7 or 10 days if no complications have been observed and some went even so far as to find bed rest unnecessary. Shah<sup>4</sup> while concluding that physical activity after myocardial infarction was associated with reduced mortality, noted that there was also association with increasing effort intolerance between 18 months and two years after the acute attack. This delayed disability of those patients who did not follow the conventional bed rest was not explained by the author. Abraham and co-workers in a prospective randomized study came to the unusual conclusion that early mobilization is beneficial irrespective of

complications on admission in patients with acute myocardial infarction. Hurst, on the other hand, in an Editorial in the same issue scrutinizes the article by Abraham and colleagues and finds certain deficiencies in the type of investigation these authors followed in their study and concludes that common sense dictates that patient management should be individualized and that this matter is under active study by many people. Mather and associates even considered home care preferable for many patients particularly older ones and—strangely enough—for those with initial hypotension. Wingo and Lopez found early ambulation even beneficial in patients admitted with complications. Collins maintains that the decision whether hospital or home care is desirable depends on the status of the patient two hours after the start of symptoms. Some other investigators arrive also at remarkable conclusions. Wilson and Pantridge base the early discharge from the hospital of their patients on the degree of the R-S-T segment displacement. Earlier studies, however, have demonstrated in experiments on dogs that very small and superficial lesions of the heart for instance brushing a 10 per cent solution of sodium chloride on an area as large as one square centimeter or mechanical lesion of such an area may cause a marked displacement of the R-S-T segment. Chaturvedi and colleagues discharged from the hospital 68 per cent of their patients with acute myocardial infarction by the seventh day. However, persistence of R-S-T elevation of more than two millimeters six days after the onset of the infarction argues against an early discharge.

In an Editorial it is stated that in a majority of uncomplicated infarctions, immobilization for more than seven days is not justified. Hayes and co-workers removed from the coronary care unit after 48 hours patients when they were free of pain, heart failure and arrhythmias. These patients were discharged from the hospital nine days after the onset of the infarction. However, such patients not rarely develop later transmural infarctions.

Despite the numerous studies mentioned above we are convinced that early mobilization and discharge from the hospital of patients with acute myocardial infarction is associated with more frequent complications particularly congestive heart failure and ventricular aneurysm. It is established that the amount of circulating blood increases when patients change from complete bed rest to even slight physical activity due to sudden mobilization of blood from the depot; this increased circulating blood volume returns to the heart and bulging of the damaged portion of the myocardium is understandable. This would not occur in small subendocardial infarctions but in transmural infarctions readily recognized in the electrocardiogram the situation is different. The point must be stressed that the clinical diagnosis of cardiac aneurysm even with the aid of the X-ray studies is very difficult and often missed (unless one uses invasive procedure). In addition sudden dilatation of the heart may lead to congestive heart failure.

Because of the many papers of recent vintage recommending a short stay in the hospital of patients with acute myocardial infarction, Utilization and Peer Review Committees insist on quick discharge of such patients. The decision is often made within the first hours after admission of the patient without regard to later developments.

Repeatedly we observed patients with acute myocardial infarction who after discharge from the hospital developed

gallop rhythm, distant muffled heart sounds and pulmonary congestion. These patients improved markedly when in addition to medication rest (not absolute bed rest) was recommended for several weeks or even months. Some of these patients remained symptom free for years afterward.

It must be stressed that not every clinician finds an early mobilization of patients with acute myocardial infarction justifiable. Thus Blumgart and Zoll sound a warning directed toward the advocates of early mobilization and "emphasize the importance of rest and reduced activity for many weeks after acute myocardial infarction." Weingarten and colleagues observed 35 patients with acute myocardial infarction for 4 to 14 months after early discharge from the hospital. All had been mobilized by the sixth day and were discharged after up to 15 days after hospitalization. Two of these patients were readmitted because of a new infarction, two developed congestive heart failure and one of these died. In another study the recurrence of myocardial infarction within months after dismissal from the hospital of patients who were ambulated early was very high. In a recent Editorial "Miller" takes a compromise attitude when he assumes that "around three weeks of hospitalization offers a reasonable middle route to follow" and emphasizes that "It remains to be established whether there is any value to early mobilization other than the psychological benefit."

Generalizations on this subject are not justified. Sensible individualization is necessary and every patient has to be evaluated according to the clinical findings.

Our tentative suggestions are as follows: For small "intramural" or subendocardial infarctions, without complications we recommend one week of bed rest and discharge from the hospital after 14 to 20 days. In larger and especially transmural infarctions, without complications, we advise bed rest of three to four weeks and discharge in four to five weeks. Any significant complication will cause lengthening of the time of bed rest and hospital stay. It is well recognized that complications may arise suddenly and unexpectedly even in the mildest case, namely in patients with a "small" infarction.

David Scherf, M.D.

55 E. 86th Street

New York, N.Y. 10028

Jules Cohen, M.D.

Department of Medicine

New York Medical College

New York, N.Y.

# REFERENCES

1. Lewis T. Diseases of the heart. 2nd edition. London 1937. MacMillan and Co. p. 49.
2. Karsner H. T. and Dwyer J. E. Jr. Studies in infarction IV. Experimental bland infarction of the myocardium myocardial regeneration and cicatrization. J. Med. Res. 34: 21 1916.
3. Mallory G. K. White I. D. and Salcedo Salazar J. The speed of healing of myocardial infarction. AM HEART J. 18: 647 1939.
4. Jetter W. W. and White P. D. Rupture of the heart in patients in mental institutions. Ann Intern Med. 21: 783 1944.
5. Sutton D. C. and Davies M. D. Effects of exercise on experimental myocardial infarction. Arch Intern Med. 48: 1118 1931.
6. Thomas W. C. and Harrison T. R. The effects of

It is our proposal that the observed reaction of dispersal followed by aggregation is a function of the surface active properties of the heparin coumadin etc molecules acting on the surfaces of cells and the surfaces of other particles present in the blood. Heparin or other surfactant molecules accumulating at the cell surfaces form films adjacent films then adhere to each other causing aggregation to occur. Albumin and fragments of cells are also capable of layering out on surfaces to form films and in a manner similar to that exerted by high concentrations of heparin to produce aggregation. The point to be emphasized is that to prevent particle aggregation an optimal concentration of the anticoagulating or antiaggregating agent must be present in the circulating blood during the bypass procedures. Optimal is used to mean

that concentration of drug at which dispersion has fully occurred and beyond which aggregation will be initiated. The concentration can be quickly and empirically determined through microscopic examination of blood samples which are routinely drawn during bypass surgery.

Bernard Ecanou Ph.D  
Bernard H Gold Ph.D  
University of Illinois  
at the Medical Center  
Chicago, IL  
Max Sadove M.D.  
Rush Medical Center  
Chicago, IL

## To each according to his desert

Bed rest is one measure which is generally used in the management of a patient with acute myocardial infarction. The length of bed rest of such patients varied a great deal with the passage of time. According to Lewis, rest in bed should be continued for at least eight weeks even in the milder cases to ensure firm cicatrization of the ventricular wall. A number of patients have lost their lives and especially those who have early recovered from symptoms by neglect of these precautions. Most authors recommended a bed rest of six weeks duration. This is a far cry from the few days of bed rest advocated lately. The long bed rest in general use was influenced by a few experimental studies performed by pathologists.

As early as 1916 Karsner and Dwyer<sup>1</sup> had found necrotic tissue in the myocardium 60 days after ligation of a coronary artery in dogs. More than two decades later Mallory White and Salcedo Salzar<sup>2</sup> in their classical paper showed that it took five weeks for the removal of necrotic material after an infarction. While small infarctions in dogs healed in about five weeks, large ones healed completely in two months. Therefore to every clinician the long bed rest for patients with acute myocardial infarction seemed to be absolutely necessary. This viewpoint found support in a study which revealed a higher incidence of rupture of the myocardium in mental patients with acute myocardial infarction who were ambulatory. 73 per cent of patients with an acute myocardial infarction died from cardiac rupture and tamponade. Furthermore experiments on dogs<sup>3</sup> showed that after ligation of the ramus descendens anterior rest led to healing of the infarction with production of a small firm scar without thinning of the ventricular wall while early exercise (within three days after the operation) resulted in thin scars with aneurysmal bulging.

The often quoted experiments by Thomas and Harrison are not pertinent because the myocardium was only slightly damaged by burning; the authors themselves caution not to draw conclusions concerning patients.

For many years now perhaps influenced by statements pointing out the harm done by prolonged bed rest, patients

with acute myocardial infarction were asked to be out of bed early and were discharged early from the hospital. Already in 1959 Brummer and colleagues questioned the need for long bed rest in the management of acute myocardial infarction. Groden and associates did not find any significant difference in mortality rate, development of hypotension, shock or heart failure, further episodes of chest pain, incidence of arrhythmias in two groups of patients with acute myocardial infarction when mobilized early or late and discharged from the hospital early or late. The authors also state that there was no difference in the long term incidence of ventricular aneurysms in the two groups. One of their groups stayed in the hospital three weeks and the other five weeks.

In addition to venous thrombosis and pulmonary embolism, muscular atrophy, economic and psychologic effects were mentioned as arguments against prolonged bed rest. This completely disregarding the findings of pathologists mentioned above, it is also significant with today's reliance on instrumental findings that in more recent studies the presence or absence of gallop rhythm, distant muffled heart sounds, râles over the bases of the lungs, often even the level of blood pressure are not considered in a decision of the duration of bed rest.

In numerous recent studies more authors tried to demonstrate that still earlier ambulation and earlier discharge from the hospital did not increase mortality and morbidity and did not lead to the formation of a cardiac aneurysm. Some authors discharge patients with acute myocardial infarction even after 7 or 10 days if no complications have been observed and some went even so far as to find bed rest unnecessary. Shah, while concluding that physical activity after myocardial infarction was associated with reduced mortality, noted that there was also association with increasing effort intolerance between 18 months and two years after the acute attack. This delayed disability of those patients who did not follow the conventional bed rest was not explained by the author. Abraham and co-workers in a prospective randomized study came to the unusual conclusion that early mobilization is beneficial irrespective of

Table 1 Expected mortality for cohort

| Age (years) | n     | Mortality p | np   | Risk factors |      | Adjusted mortality |      |
|-------------|-------|-------------|------|--------------|------|--------------------|------|
|             |       |             |      | f            | f    | np/f               | np/f |
| < 29        | 5540  | 18          | 010  | 84           | 5.00 | 01                 | 02   |
| 30-39       | 2,393 | 20.5        | 049  | 7.3          | 4.50 | 0*                 | 11   |
| 40-49       | 1439  | 122.0       | 171  | 6.27         | 4.00 | 2.                 | 13   |
| 50-59       | 463   | 403.0       | 1.85 | 4.96         | 3.21 | 37                 | 58   |
| 60-64       | 79    | 841.0       | 0.66 | 4.36         | 1.74 | 15                 | 38   |
| 64-69       | 3*    | 1234.0      | 0.39 | 3.76         | 1.87 | 10                 | *1   |
| > 0         | 12    | 1704.0      | 0.17 | 3.16         | 1.99 | 05                 | 16   |
| Total       | 9958  | 186.0†      | 5.37 | 5.19         | 2.86 | 10.                | 1.89 |

†A stage f all ages.

the expected mortality rate per year for this group. Columns 5 and 6 indicate the smoking weight combined risk factors computed with slightly different assumptions for each column. The two final columns present the annual mortality rate expected for the 9958 men who do not smoke and are less than 90 per cent of average adjusted weights. We see that we may anticipate one or two deaths per annum from ischemic and related heart disease.

It is clear that statistics which under alternative initial conditions (marathoners vs a non smoking thin non running age adjusted control group) achieve only a difference of 1 or 2 deaths per year (and this difference requires the assumption that marathoners confers absolute protection) are statistics that are not able to assess meaningful differences in the risk factors appropriate to the two groups. I must conclude that only a formal long term prospective epidemiological study that utilizes an appropriate control group can be expected to provide a data base from which valid conclusions can be extracted.

Paul Wilby Ph.D  
Environmental Sciences Laboratory  
Department of Community Medicine  
Mount Sinai School of Medicine  
New York N.Y. 10029

## REFERENCES

- 1 Keys A. Physical activity and the epidemiology of coronary disease. In: Brunner D. Ed. Physical activity and aging. Medicine and sport vol IV. Baltimore 1970. University Park Press p 200.
- 2 Keys A. Coronary heart disease—the global picture. Atherosclerosis 22:149 1970.
- 3 Fox S M III. Physical activity and coronary heart disease in controversy in cardiology. ed E. K. Chang. New York 1976. Springer Verlag pp 201-219.
- 4 Bassler T J. Letter to the Editor. Lancet 2:711 1972.
- 5 Bassler T J. Long distance runners. Science 128:1083 1973.
- 6 Young K. US Distance Rankings for 1970. National Running Data Center. University of Arizona, Tucson Ariz. 1975.
- 7 Statistical Bulletin. Socioeconomic Mortality Differentials. Metropolitan Life Insurance Co. January 1975.
- 8 Hammond E C and Garfinkel L. Coronary heart disease: stroke and aortic aneurysm. Arch. Env. Health 19:167 1969.
- 9 Hammond E C. Smoking in relation to the death rates of one million men and women. National Cancer Institute Monograph No 19 pp 127-204. January 1966.

## Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author: The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.



- artificial restriction of activity in the recovery of rats from experimental injury *Am J Med* 208 436 1944
- 7 Scherf D and Boyd J J Cardiovascular Diseases J II Lippincott Philadelphia 1947 p 68
  - 8 Dock W The evil sequelae of complete bed rest *JAMA* 125 1083 1944
  - 9 Brummer P Linko E and Hasanen A Myocardial infarction treated by early ambulation *Am HEART J* 52 269 1956
  - 10 Groden B M Allison A and Shaw G H Management of myocardial infarction *Scot Med J* 12 435 1967
  - 11 Audge A A J Prognosis after early discharge from hospital of patients with acute myocardial infarction *Br Heart J* 31 750 1969
  - 12 Harpur J E Kellett R J Conner W T et al Controlled trial of early mobilisation and discharge from hospital in uncomplicated myocardial infarction *Lancet* 2 1331 1971
  - 13 Duke M Bed rest in acute myocardial infarction *Am HEART J* 82 486 1971
  - 14 Irvin C W and Burgess A M The abuse of bed rest in the treatment of myocardial infarction *N Engl J Med* 243 486 1950
  - 15 Shah J R Letter—Early mobilisation after myocardial infarction *Lancet* 1 534 1972
  - 16 Abraham A S Sever J Weinstein M Dallberg M and Mencil J Value of early ambulation in patients with and without complication after acute myocardial infarction *N Engl J Med* 292 719 1975
  - 17 Hurst J W Editorial—Ambulation after myocardial infarction *N Engl J Med* 292 746 1975
  - 18 Mather H G Morgan D C Pearson N G and al Myocardial infarction A comparison between home and hospital care for patients *Br Med J* 1 925 1976
  - 19 Wingo C S and Lopez A Ambulation after myocardial infarction *N Engl J Med* 294 341 1976
  - 20 Collins A Home or hospital care after myocardial infarction Is this the right question? *Br Med J* 1 559 1974
  - 21 Wilton C and Pantidge J F ST segment displacement and early hospital discharge in acute myocardial infarction *Lancet* 2 1284 1973
  - 22 Boyd L J and Scherf D The electrocardiogram in experimental pericardial (epicardial) injury *Bull N Y Med Coll* 2 168 1939
  - 23 Chaturvedi N E Walsh M J, Evans A et al Selection of patients for early discharge after acute myocardial infarction *Br Heart J* 36 533 1974
  - 24 Editorial Myocardial infarction then and now *Lancet* 1 330 1974
  - 25 Hayes M J Morris G K and Hampton J H Comparison of mobilisation after 2 and 9 days in uncomplicated myocardial infarction *Br Med J* 3 10 1974
  - 26 Madigan N P Rutherford H D and Frye R L The clinical course early prognosis and coronary anatomy of subendocardial infarction *Am J Med* 60 634 1976
  - 27 Mater H G Pearson N G Read K L Q et al Acute myocardial infarction Home and hospital treatment *Br Med J* 3 334 1971
  - 28 Blumgart H L and Zoll P M Clinical pathologic correlations in coronary artery disease *Circulation* 47 1139 1973
  - 29 Weingarten M A Pinkhas J and de Vries A Early discharge after myocardial infarction *Folia Clin Int (Bar.)* 25 271 1975
  - 30 Miller A J Editorial—Rehabilitation and length of hospitalization after acute myocardial infarction *Am HEART J* 92 547 1976

## Statistics, marathoning and CHD

Many reports have appeared in the last decade that describe epidemiological studies of the relationship between physical activity and mortality especially mortality from coronary heart disease. The methodological and epidemiological problems encountered by these studies are extreme and valid conclusions are notoriously difficult to achieve. Yet Bassler has written that a search of the literature failed to document a single death due to coronary arteriosclerosis among marathon finishers and in a subsequent letter he concludes that when the level of vigorous exercise is raised high enough the protection appears to be absolute. The American Medical Joggers Association has been unable to document a single death resulting from coronary heart disease among marathon finishers of any age. We do not know what significance we are to place upon Bassler's communications: we do not know how many deaths of marathoners—from all causes—was revealed by the search of the literature conducted by Bassler nor do we know the number of autopsies performed or reviewed by the A.M.J.A. both crucial facts for establishing the statistical significance of his findings.

I have made some calculations which bear on this. In 1975 10 482 men and women completed a marathon road race. Approximately 11 per cent of these runners were women leaving 9 958 male marathoners. I have estimated the number of men expected to die from ischemic and related heart disease in a cohort of 9 958 white American males whose age distribution is the same as these marathoners but whose relative weight level of exercise and smoking habits are the same as the general American insured male population. However, marathoners almost to a man (or to a woman) are invariably quite thin and not addicted to smoking. After applying appropriate weight and smoking risk factor corrections to the estimated mortality rate for these men, we may obtain an estimate of the number of men that would be expected to die per year in this non running non smoking non average weighted group of men. This estimate then is independent of any postulated protection that marathoning might afford. Table 1 columns 1 and 2 show the age distribution of the marathoners, column 3 the annual mortality rate per 10 for each age interval for white insured U.S. males and column 4



Fig 1 Mutilation of SA nodes which occurred during autopsy thereby impairing the study of two interesting cases—one from Italy and one from Portugal. (Hematoxylin and eosin  $\times 10$ )

Thorough histologic study of the pacemaker is always hampered by these injuries and sometimes impeded. Surely it is nonsensical to sacrifice the very heart a heart on the autopsy table to mere manual habit.

One can avoid any damage to the SA node by simply extending the lateral incision of right ventricle and AV ring posteriorly into the ostium of the inferior vena cava instead of the superior. Through this wide gap the inner atrial wall can be inspected. It can be turned inside out, the intercaval bridge can be further cut lengthwise as medially as possible.

Suggestions have been put forward on the matter without apparent success. A strong authoritative and far reaching plea to salvage the pacemaker at autopsy is needed in order to secure basic morphologic knowledge in the field of arrhythmias.

Lino Rossi  
Via Annunziata 23/4  
Milan Italy

#### REFERENCES

- 1 American Hospital Association. Postmortem procedures, 1970.
- 2 Redaelli P. Guida all'autopsia. Milan 1950.
- 3 Rossi L. Histopathologic features of cardiac arrhythmias. Milan 1969.

#### Reactions to furosemide

##### To the Editor

In the July 1977 issue of THIS JOURNAL (94:6 1977) Dr Greenblatt and colleagues conclude that furosemide is a relatively safe diuretic in a wide range of clinical situations, based on the observation of a 10.1 per cent incidence of adverse reactions among 2,367 hospitalized patients in whom only two deaths were felt to be furosemide related. They found the data reassuring since serious toxicity was unusual.

While not necessarily disagreeing with their conclusions, we would like to point out that the authors' criteria for serious toxicity are not mentioned in the article. In addition, it is not clear how aggressively possible reactions were sought. Were audiograms routinely performed before and after furosemide

therapy or was the patient required to complain of hearing difficulties? There is abundant literature implicating furosemide as a potentially ototoxic drug. Were the drugs whose toxicities are known to be potentiated by furosemide such as cephaloridine, lithium, aminoglycoside antibiotics, and curan form drugs included in the tabulation?

There were 370 patients in the report who carried a diagnosis of "congestive heart failure" and 164 patients "acute myocardial infarction." As is pointed out in a recent article edited by one of the investigators, patients with chronic congestive heart failure have been noted to have decreased blood pressure and cardiac output with elevated systemic vascular resistance. "Diuretics may be effective but are very likely to decrease cardiac output further and to impair renal function still more." In acute myocardial infarction, sudden massive diuresis in patients with normal filling pressures might be expected to reduce cardiac output and adversely affect the myocardial oxygen supply/demand balance. We wonder how carefully hemodynamic parameters were monitored in the reported patients. Volume depletion was cited as the commonest adverse reaction based on the finding of elevated blood urea nitrogen in many cases. Were indices of creatinine clearance monitored too? Patients with many of the illnesses represented have in our experience diminished appetite and protein intake. Consequently blood urea nitrogen might not be a sensitive measure of volume status or nephrotoxicity.

In summary, we do not disagree with Dr Greenblatt and associates' enthusiasm for furosemide as a safe diuretic. However, we do not feel that their article has proved the conclusions stated. It should be recalled that 16.3 per cent of their patients died during hospitalization. Moreover, how many receiving furosemide as outpatients suffered consequences in the unsupervised milieu at home is not clear. We believe that the potent loop diuretics should still be respected and that appropriate monitoring for adverse effects should accompany their use.

Lieutenant S E Warren (MC) USNR  
Commander S M Steinberg (MC) USN  
Nephrology Division  
Department of Internal Medicine  
Naval Regional Medical Center  
San Diego, California 92161

The opinions and assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the view of the Medical Department of the Navy or the Naval Service at large.

#### REFERENCES

- 1 Vargish T, Benjamin H and Shenkman L. Deafness from furosemide. Ann Intern Med 72:761 1970.
- 2 Schwartz G H, David D M, Riggio R R et al. Ototoxicity induced by furosemide. N Engl J Med 282:1413 1970.
- 3 Wigand M H et al. Ototoxic side effects of high doses of furosemide in patients with uraemia. Postgrad Med J 47(Suppl) 54 1971.
- 4 The Medical Letter 19 No 2, Jan '78 1977.
- 5 Cohn J N and Franciosa J A. Drug therapy: Vasodilator therapy of cardiac failure (edited by Koch Waser J). N Engl J Med 297:255 1977.

## Needed An FDA for surgery?

To the Editor

If heart attacks were caused by germs it properly would be said that we the people are in the midst of a raging epidemic of a highly lethal disease. If the medical profession advised for the treatment of this epidemic the widespread use of an incredibly expensive painful treatment having a small but definite mortality rate of its own and yet a treatment which had not yet been proved to prolong life in the great majority of cases it properly could (and would) be said of us that we are a bunch of fools. This precisely is the state of affairs today for coronary bypass surgery. If a wise and dispassionate onlooker were to say that there must be a better way, he would be right. There is.

Much public agitation occurred recently when the popular press reported the results of a scientific study which purported to demonstrate that coronary bypass surgery does not prolong life. While the validity of this conclusion is open to some question, what is not open to question is that this kind of proof is being sought years too late.

Insofar as drugs are concerned, the medical community long has taken the position and rightly so that the burden of proof is on the protagonist who claims safety and efficacy for a new drug. Right from the beginning it is up to the drug manufacturer to prove that his drug works and that the risk of taking the drug is less than the risk of having the untreated disease. Until he does so, the drug is prohibited by the FDA from being sold on the open market. Undoubtedly some lives may be lost by such a cautious approach, but the attitude of our profession is when in doubt an error of omission is better than an error of commission. Above all do no harm is a venerable and deeply held medical axiom.

Unfortunately this policy rarely, if ever, is followed for surgical procedures. A new operation, no matter how bizarre, often can be championed by a surgeon without any proof whatsoever other than his intuitive (and often erroneous) experience. If the hospital medical staff and administration are compliant, as first tens, then hundreds, and finally thousands upon thousands of these operations are done, bits and pieces of positive and negative information are accumulated, but more often than not, even then a firm scientific foundation for the operation still cannot be given.

This is the present sad state of affairs for coronary bypass surgery. Ten years down the line and after tens of thousands of operations have been performed, only recently are we asking for the kind of rigid scientific proof that should have been demanded right from the start. If (as seems probable) a suitable animal model could not have been fashioned, then the procedure should have been labeled an experimental procedure and handled in the same way as a new and unproved drug would have been handled. The initial trials should have been limited to a few authorized hospitals which were prepared to conduct these trials under strict scientific conditions, conditions calculated to yield the maximum amount of information with the least risk to the patients.

Let this experience be a lesson to us. Henceforth we should

require of new surgical procedures what we now require of new drugs. Our bull dog posture should be: Show me!

Myron R. Schoenfeld, M.D.

21 Oerthill Rd.

Scarsdale, N.Y. 10583

The author is a cardiologist who prefers to make as few errors of commission as possible.

## Fructose and triglycerides

To the Editor

In an Annotation in your JOURNAL of December 1974, Roberts calls attention to the relation between dietary sucrose and triglyceride levels. It is interesting to note that papers published by other authors show that this action is due to fructose.<sup>1-3</sup> Our previous work showed that it is possible to know the reaction of the patients by means of a load of 100 gm of fructose.<sup>4</sup> With this procedure it is possible to know if the patients need a restriction of sucrose in the diet.

M. J. Halpern

Department of Biochemistry

Institute of Biomedical Sciences

Campo de Santana

Lisbon, Portugal

## REFERENCES

1. Cook G. C. Absorption and metabolism of D( ) fructose in man. *Am J Clin Nutr* 24:1302, 1971.
2. MacDonald I. and Turner L. J. Serum glucose and fructose levels after sucrose meals in atherosclerosis. *Nutr Metab* 13:168, 1971.
3. Halpern M. J. and Miguel M. J. Fructose and uric acid. *Lancet* i:670, 1973.
4. Halpern M. J. Saccharides and triglycerides. *Am J Clin Nutr* 26:687, 1973.

## Salvage the pacemaker at autopsy

To the Editor

Frequently I receive autopsy material from various sources both Italy and abroad for *claucomatologic* control of the conducting system. It is most distressing to note how often serious injury has been inflicted on the cardiac specific tissue by the customary postmortem procedures in the hands of pathologists who have not been warned or who do not specialize in cardiac tissue. All too often the sinoatrial (SA) node (Fig. 1) has been badly slashed by the traditional handbook incision, driven alongside the right atrioventricular (AV) walls and positioned laterally in the superior vena cava. Often there is a lengthwise cut in the intercaval bridge as well.

**Recent Advances in Vascular Diseases** Edited by Arnold Kappert Hans Jorg Leu and Peter Waibel Bern Stuttgart Vienna 19 ■ Hans Huber Publishers 159 pages Price \$9.75

This paperback book contains all the papers published in English during 1975 in *VASA*, a journal devoted to vascular diseases. The papers are grouped according to subjects namely microcirculation research angiography and clinical practice. This book should interest all physicians and surgeons who treat peripheral vascular disease since the various papers are diversified and would interest anyone. There is a need to learn more about peripheral vascular diseases and to realize more fully that the principles of peripheral vascular physiology and peripheral vascular disease states apply to the vascular system of all organs not only to that of the limbs. Peripheral vascular diseases are common and need more serious consideration in training programs in medicine especially cardiovascular training programs. *VASA* is a journal that needs more attention by practicing physicians. The editors of this book have provided a fine service to physicians and trainees as well as to the journal *VASA*.

**Mechanical Support of the Failing Heart and Lungs** Edited by David Bregman New York, 1977 Appleton Century Crofts 210 pages

Bregman and the 28 contributing authors have produced a book of seven chapters with appended discussions on a special and highly technical procedure. The use of circulatory support in its developmental stages at present. Those in the field both clinical and research will find this book of considerable value to them while those in cardiology will need this book as a source of information concerning the thinking of the contributors. The discussions are interesting and reveal the limitations in the present state of knowledge and techniques. This book is concerned with a highly specialized procedure which is of more than cursory interest to only a few cardiovascular surgeons and cardiologists.

**Pathophysiology Diagnostic Therapy—Herzkrankheiten** Edited by H. Reindell and H. Roskamm Berlin 1977 Springer Verlag ■ 111 pages. Price \$36.60

Reindell and Roskamm have edited a textbook on heart disease with emphasis on pathophysiology diagnosis and

treatment and which integrates these three aspects of clinical cardiology extremely well. The approach is different from most textbooks on heart disease in that the mechanism of disease is constantly related to the clinical syndromes discussed throughout the book. The brief descriptions of anatomic and physiologic peculiarities of the cardiac pump are well supported by well selected illustrations. Chapters on the more sophisticated diagnostic techniques are good and include phonocardiography arterial and venous blood pressure recording vectorcardiography echocardiography coronary angiography and impedance plethysmography among others. Even though the book contains almost one thousand pages the two editors and other contributors present only selected aspects of cardiology.

Since this book emphasizes pathophysiology pathology and hemodynamic phenomena so well it should serve as an excellent supplement to the existing books which are less concerned with these important aspects of cardiology. The book should be translated into English in order to reach a larger audience. Furthermore physiologists and pathologists who teach medical students will find the book to be useful in planning their course presentations in cardiology and hemodynamic physiology. The book is highly recommended to medical students as well as to those training in and practicing cardiology. It must be added that the publishers have done an excellent job in the production of this book.

**Case Studies in Echocardiography A Diagnostic Workbook** By Ralph D. Clark M.D. Philadelphia 1977 W. B. Saunders Company 334 pages Price \$14.95

Clark's case study book on echocardiography is a very good publication on the subject. The cases are well selected and the discussions are good. The illustrations are a little blurry but adequate for study. Readers will find this book to provide them not only with an opportunity to learn ECHO but to compare their interpretations and recording technique with Clark's. The discussions are good, but without the entire strip of recording the sections selected do handicap interpretations. This is well illustrated by Case 37. Nevertheless readers who patiently study each case will profit immeasurably by this book. The section on measurements and calculations is useful for beginners as well as for experienced echocardiographers. This is a valuable addition to this rapidly expanding diagnostic procedure in cardiology.

## Reply

### To the Editor

Our paper on adverse reactions to furosemide cited several references<sup>1,2</sup> that describe in detail the methodology of the Boston Collaborative Drug Surveillance Program (BCDSP). The monitoring system used by the BCDSP is integrated into the routine operation of the medical ward and does not interfere with that routine. All decisions regarding diagnostic tests and therapeutic measures are made by house staff or attending physicians responsible for the care of these patients and are based solely upon clinical needs. The recording of an adverse drug reaction, defined as an unintended or undesired drug effect, is also based upon the clinical judgment of treating physicians, later corroborated by a clinical pharmacologist who reviews the case. In most instances, these adverse drug reactions are of sufficient clinical importance to necessitate drug discontinuation, alteration of dosage, or institution of some specific therapeutic measure. We realize that certain limitations and uncertainties are inherent in this approach to comprehensive drug surveillance. However, the 11 year experience

of the BCDSP, which now involves more than 35,000 hospitalized medical patients, indicates that the data provide a reasonably accurate description of clinical drug effects in this setting.

David J. Greenblatt, M.D.  
Boston Collaborative Drug Surveillance Program  
400 Totten Pond Rd.  
Waltham, Mass. 01154

## REFERENCES

1. Miller R. R. and Greenblatt D. J. Editors. *Drug Effects in Hospitalized Patients: Experiences of the Boston Collaborative Drug Surveillance Program 1966-1975*. New York 1976. John Wiley & Sons.
2. Allen M. D. and Greenblatt D. J. Role of nurse and pharmacist monitors in the Boston Collaborative Drug Surveillance Program. *Drug Intell Clin Pharmacol* 9:648, 1975.
3. Jick H. Drugs—remarkably nontoxic. *N Engl J Med* 291:824, 1974.

## Book reviews

**Recent Advances in Vascular Diseases** Edited by Arnold Happort Hans Jorg Leu and Peter Waibel Bern Stuttgart Vienna 1976 Hans Huber Publishers 159 pages Price \$39.75

This paperback book contains all the papers published in English during 1975 in *VASA* a journal devoted to vascular diseases. The papers are grouped according to subjects namely microcirculation research angiography and clinical practice. This book should interest all physicians and surgeons who treat peripheral vascular disease since the various papers are diversified and would interest anyone. There is a need to learn more about peripheral vascular diseases and to realize more fully that the principles of peripheral vascular physiology and peripheral vascular disease states apply to the vascular system of all organs not only to that of the limbs. Peripheral vascular diseases are common and need more serious consideration in training programs in medicine especially cardiovascular training programs. *VASA* is a journal that needs more attention by practicing physicians. The editors of this book have provided a fine service to physicians and trainees as well as to the journal *VASA*.

**Mechanical Support of the Failing Heart and Lungs** Edited by David Bregman New York 1977 Appleton Century Crofts 210 pages

Bregman and the 28 contributing authors have produced a book of seven chapters with appended discussions on a special and highly technical procedure. The use of circulatory support is in its developmental stages at present. Those in the field both clinical and research will find this book of considerable value to them while those in cardiology will need this book as a source of information concerning the thinking of the contributors. The discussions are interesting and reveal the limitations in the present state of knowledge and technique. This book is concerned with a highly specialized procedure which is of more than cursory interest to only a few cardiovascular surgeons and cardiologists.

**Pathophysiologie Diagnostik Therapie—Herzkrankheiten** Edited by H. Reindell and H. Roskamm Berlin 1977 Springer Verlag 830 pages. Price \$56.60

Reindell and Roskamm have edited a textbook on heart disease with emphasis on pathophysiology diagnosis and

treatment and which integrates these three aspects of clinical cardiology extremely well. The approach is different from most textbooks on heart disease in that the mechanism of disease is constantly related to the clinical syndromes discussed throughout the book. The brief descriptions of anatomic and physiologic peculiarities of the cardiac pump are well supported by well selected illustrations. Chapters on the more sophisticated diagnostic techniques are good and include phonocardiography arterial and venous blood pressure recording vectorcardiography echocardiography coronary angiography and impedance plethysmography among others. Even though the book contains almost one thousand pages the two editors and other contributors present only selected aspects of cardiology.

Since this book emphasizes pathophysiology pathology and hemodynamic phenomena as well it should serve as an excellent supplement to the existing books which are less concerned with these important aspects of cardiology. The book should be translated into English in order to reach a larger audience. Furthermore physiologists and pathologists who teach medical students will find the book to be useful in planning their course presentations in cardiology and hemodynamic physiology. The book is highly recommended to medical students as well as to those training in and practicing cardiology. It must be added that the publishers have done an excellent job in the production of this book.

**Case Studies in Echocardiography A Diagnostic Workbook** By Ralph D. Clark M.D. Philadelphia 1977 W. B. Saunders Company 334 pages Price \$14.95

Clark's case study book on echocardiography is a very good publication on the subject. The cases are well selected and the discussions are good. The illustrations are a little blurry but adequate for study. Readers will find this book to provide them not only with an opportunity to learn ECHO but to compare their interpretations and recording technique with Clark's. The discussions are good, but without the entire strip of recording the sections selected do handicap interpretations. This is well illustrated by Case 37. Nevertheless readers who patiently study each case will profit immeasurably by this book. The section on measurements and calculations is useful for beginners as well as for experienced echocardiographers. This is a valuable addition to this rapidly expanding diagnostic procedure in cardiology.

**Physiology for the Anesthesiologist** By Nishan G Goudsouzian and Agop Karamanian New York 1977 Appleton Century Crofts 388 pages Price \$22 50

**Pulmonary Pathophysiology, the Essentials** By John H West M D Ph D Baltimore 1977 The Williams & Wilkins Company 198 pages Price \$9 95

**Infectious Diseases** 2nd edition Edited by Paul D Hoepfich M D Hagerstown Md 1977 Harper & Row Publishers Inc 1258 pages Price \$42 50

**Respiratory Disease** Edited by D J Lane New York 1977 Appleton Century Crofts 553 pages Price \$28 50

**High Risk Pregnancy and Child** By Z Stembera K Znamenscek and K Polacek Littleton Mass 1977 PSG Publishing Co Inc 307 pages Price \$25 00

**The Hemoglobinopathies Techniques of Identification** By Titus H J Hausman and J H P Jonxis New York 1977 Marcel Dekker Inc 464 pages Price \$44 00

---

## Announcements

---

### Health Sciences Communications Association meeting

The twentieth annual Health Sciences Communication Association meeting will be held in May 1978 in Tucson Arizona. The program title is *HeSCA del Sol*. The Communications Spectrum, HeSCA communications activities will be viewed in their relation to Among Professional Specialties, Beyond Institutional Walls, Across the Community and Culture, and Over National Boundaries. For further information regarding this meeting contact Beverly Hill Chairperson Promotion Committee Director of Biocommunications School of Pharmacy, 1985 Zonal Ave, Los Angeles Calif 90033.

### American College of Nutrition meeting

The 19th Annual Meeting of the American College of Nutrition will be held in Minneapolis on June 1 and 2 1978 at the Radisson South Hotel. The theme for this interdisciplinary international organization this year will be Cardiovascular Diseases and Nutrition. Plenary sessions will be concerned with the etiological mechanisms of nutrition inherent in cardiovascular disease, primarily atherosclerosis as well as dietary, drug and surgical modifications in therapy. In addition, the scientific paper sessions invite the submission of free communications. For further information please contact Ms Faith Jermon, Executive Secretary, American College of Nutrition, P O Box 85 669 Boston Post Road, Guilford Conn 06437 or Continuing Medical Education, University of Minnesota, Box 293 Mayo Memorial Building, 420 Delaware Street SE, Minneapolis, Minn 55455.

### Postgraduate course in Angiography and Vascular Disease

The San Diego Radiology Research and Education Foundation and the American College of Radiology will co-sponsor a postgraduate course in Angiography and Vascular Disease on September 18 through 21 1978 at the Holiday Inn at the Embarcadero, San Diego, California.

The course is designed for clinicians, surgeons and radiologists interested in vascular disease. An interdisciplinary approach to vascular disease will be presented, integrating basic reviews and recent advances. Emphasis is on interaction between angiography, other diagnostic modalities, recent clinical advances and therapeutic concepts. For further information and registration materials please write: Angiography and Vascular Disease, P O Box 2763, La Jolla, Calif 92038.

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore, all manuscripts must be accompanied by the following statement, signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material."

## Editorial

### Ventricular afterload a succinct yet comprehensive definition

Abraham Noordergraaf Ph D M A  
Jules Melbin VMD Ph D  
Philadelphia Pa

Of the two momentous observations attributed to Starling concerned with cardiac output one was that in the heart-lung preparation with constant inflow output remained virtually independent of peripheral resistance in the physiological range. In other words cardiac output was highly insensitive to afterload a term already used by Starling.

The term afterload was introduced as a concept distinct from preload to distinguish phenomena relating to emptying in contrast to filling respectively of a cardiac chamber. In this editorial attention is focused only on ventricular ejection and we refer only to afterload.

In Starling's experiment the peripheral resistance to left ventricular ejection was controlled by adjusting the degree of collapse of a tube surrounded by air. In these experiments since flow remained constant while peripheral resistance was altered arterial pressure altered proportionally with peripheral resistance. Thus under such conditions peripheral resistance and arterial pressure served interchangeably as indicators of the load on the ventricle.

As analysis of cardiac performance progressed

to studies of the heart in situ and then to the intact heart in the conscious animal it became clear that cardiac output is in fact sensitive to afterload. This was clearly demonstrated when arterial conditions were altered such that compensatory and control phenomena were avoided hence intrinsic properties of the heart were exposed.

Consequently interest in afterload revived and the concept was analyzed in greater detail. Conceding that peripheral resistance and arterial pressure are important factors concerned with ventricular ejection many investigators have noted that it is also affected by other circulatory variables and parameters. Thus arterial compliance the inertial and viscous properties of blood and blood vessels and arterial end diastolic pressure were also attributed a role in setting the load. This complexity has been further compounded with observations of interaction of contributing elements. Examples include the pressure dependent characteristic impedance of the major arteries and the pressure dependent radius and compliance of the same vessels. The significance of the pulse wave velocity has also on occasion been stressed. Also since the load affects ejection the external work performed by a ventricle is sensitive to afterload.

In the face of current confusion it is desirable to seek a comprehensive manageable definition for afterload.

From the  $\square$  prime to  $\square$  B or governing and Ann  $\square$  B of gy U live  
mty of P n yl  $\square$  Ph  $\square$  d lpha.

S ported part by PHS gr nts HL 10 330 nd HL 19 031

Recen ed f p hucatu J ly 19 19 7

Repr t req exts Abr ham Noord gra f Ph D L i ers ty of P n  
syl ani Dept f B or governing D Ph  $\square$  d lpha, Pa 19174



The issue, however, is not simple and two fundamental concepts relating to myocardial properties should be emphasized prior to further discussion. To this end, it is convenient to utilize concepts employed with consideration of electrical energy. If a source of electrical energy operates at a constant voltage the load may be expressed in terms of the total current provided. The underlying condition then is that the voltage generated by the source is independent of the current. The counterpart of the voltage source is the current source. If the current delivered is independent of the voltage, the voltage developed becomes a measure of the load.

The properties of the heart are such that neither extreme is manifested i.e. ventricular pressure is neither independent of ejection flow nor is the converse true. Not only are such traditional sources basically unsuitable as models, further complications are introduced by the presence of valves and as a consequence of conditions varying greatly with time even during a single beat. Ejection flow by itself is not a qualified candidate for afterload owing to the interposition of the outlet valves. Also arterial parameters, taken singly or in combination fail to qualify.

The external stress, to which the myocardium is directly and continuously exposed is embodied in the intraventricular pressure. Since pressure multiplied by area constitutes force, ventricular pressure in conjunction with appropriate geometric factors of the ventricle determines the forces operating to counter myocardial shortening. Accordingly let us examine ventricular pressure as the variable which constitutes the ventricular afterload. We shall note that all other participants which have been previously identified contribute to the load so defined.

As a result of excitation-contraction coupling ventricular pressure rises initially without commencement of ejection. With rising ventricular pressure the load is seen to be increasing during isovolumic contraction. If arterial conditions are such that the outlet valves never open (as with total occlusion at the aortic root) ventricular pressure defines the time variation in the load during the complete cycle and arterial parameters are irrelevant.

Under more normal conditions the rising intra ventricular pressure soon exceeds the continuously falling central arterial pressure from

which point other factors influence afterload. For convenience let us assume that mean spatial ventricular pressure and root aortic or root pulmonary trunk pressure are equal so long as the valves remain open. If the ventricle were to eject into a large reservoir, which maintained the same pressure independent of blood injected by the ventricle or drained by the microcirculation, ventricular pressure would rise to this level and remain there. The ventricle would then experience an afterload which alters only during the isovolumic contraction phase. Since subsequently the pressure remains constant at the level set by such an arterial reservoir, while the myocardial surface area diminishes during ejection the myocardial force may decline while ejecting against the same afterload.

In the real case conditions are more complex since intracardiac pressure varies with time. The time varying pressure increase ( $\Delta p(t)$ ) at the root of the receiving artery is if linearity is assumed equal to ejection flow ( $Q(t)$ ) also a function of time, convolved with the input impedance ( $Z_i$ ) considered to be constant during a heart cycle but known to vary with heart rate\*. In analytical formulation, during ejection

$$\Delta p(t) = Q(t) * Z_i \quad (1)$$

Thus, arterial pressure at the aortic inlet  $p(t)$  and hence ventricular pressure,  $p(t)$ , become, during the ejection phase

$$p(t) = p(t) = p_{(d)} + Q(t) * Z_i \quad (2)$$

where  $p_{(d)}$  denotes the end diastolic root aortic pressure. A similar expression applies to the inlet of the pulmonary trunk.

Afterload is seen to be time variant during the entire period of systole, as a rising ventricular pressure during isovolumic contraction then during ejection by ventricular pressure according to equation 2. Afterload is thus quantified for the entire period of interest and is expressed in units of pressure or stress. Where ventricular pressure differs from root aortic pressure as is possible, for example with outflow obstruction equation 2 must be modified by an additional term to accommodate such complications.

Since the physical properties of the arterial system in any given state determine the value of

Input impedance of the systemic arteries is defined as the ratio between corresponding harmonics of the Fourier series of root aortic pressure and left ventricular ejection flow. An analogous definition applies to the pulmonary vasculature. Convolution is a mathematical procedure allowing multiplication of time dependent and frequency dependent quantities.

the input impedance (of which the total peripheral resistance is but one component) most of the quantities recommended previously as being involved with afterload find their rightful place here. When the arterial system is treated as a non-linear system, all would be included. This definition of afterload makes explicit what one would expect intuitively, i.e. the load should vary

directly with peripheral resistance and mean arterial pressure and inversely with arterial compliance.

In summary, a succinct general definition of ventricular afterload is proposed as the time-varying ventricular pressure which incorporates previously suggested definitions as constituent elements.

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following statement, signed by each author: The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

## Echocardiographic features of the normal and malfunctioning porcine xenograft valve

P A N Chandraratna, MD, MRCP

S B San Pedro, MD

Oklahoma City Okla

Prosthetic cardiac valves have been associated with a variety of cardiovascular complications.<sup>1,3</sup> Because of the low incidence of thromboembolic complications and since long term anticoagulant therapy is not required homograft and xenograft valves have been increasingly used in recent years.<sup>4</sup> Glutaraldehyde preserved porcine valves have the added advantage of a decreased incidence of valve disruption.<sup>5</sup>

The echocardiographic features of the Starr Edwards aortic and mitral prosthesis, Beall mitral valve Lillehei-Kastor valve and the Bjork Shiley aortic valve have been previously described.<sup>6-9</sup> More recently the ultrasound features of the aortic bioprosthetic valve in the mitral position were described.<sup>10</sup> The echocardiographic features of the porcine xenograft in the aortic position have not been previously reported.

We report here the echocardiographic characteristics of 23 porcine xenograft valves in the aortic or mitral position. Two patients developed serious valvular dysfunction. Abnormal echocardiographic patterns were seen in both.

### Materials and methods

Echocardiograms were performed on 30 patients with porcine xenograft valves. Three patients had both an aortic and a mitral porcine valve. Thus a total of 33 valves were studied. Technically satisfactory studies were obtained on

23 valves (from 21 patients) i.e., 70 per cent of the valves studied. Fourteen aortic valves and nine mitral valves were adequately visualized. The group consisted of 14 males and seven females and their ages ranged from 21 to 60 years. Nineteen patients were symptomatically improved after valve replacement.

Two patients with a porcine xenograft valve placed in the aortic position developed serious valvular dysfunction after valve replacement. The first patient was admitted with a low output state. The patient died ten days after the echocardiogram was performed. Autopsy revealed a markedly dilated heart and extensive thrombus formation on the valve. Six weeks after valve replacement the second patient developed staphylococcal endocarditis on the porcine valve with subsequent formation of a mycotic aneurysm of the aortic root which was confirmed by angiography and surgery.

Echocardiography was performed with the patients in the supine or left lateral decubitus position. An Ekoline 20 Ultrasonoscope with a 10 cm focus and 0.5 inch 2.25 MHz transducer, and a Honeywell 1856 or Electronics for Medicine DR8 recorder was used. In order to record the aortic prosthetic valve the transducer was usually placed in the third or fourth interspace at the left sternal border and angulated slightly medially and superiorly or inferiorly. Once the echoes from the stent of the porcine valve were clearly seen within the aortic root the recording was started and slight changes in angulation of the transducer were made until the cusps of the porcine valve were seen. It should be stressed that high coarse gain and low reject settings were usually necessary to record cusp echoes whereas to

From the Department of Medicine, Division of Cardiology, University of Oklahoma Health Sciences Center, Oklahoma City, Okla.

Received for publication Nov. 16, 1976.

Accepted for publication Jan. 18, 1977.

Reprint requests: Dr P A N Chandraratna, University of Oklahoma Health Sciences Center, P O Box 26901, Oklahoma City, OK 73190.

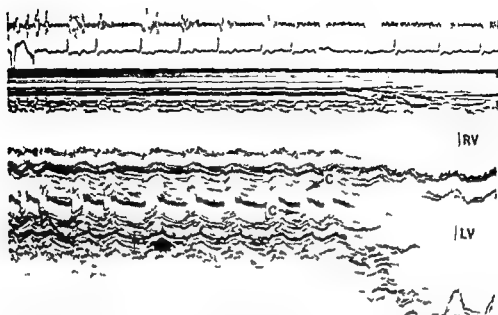


Fig 1 Sweep from aortic root to left ventricle in a patient with aortic valve replacement by a porcine xenograft valve. The parallel echoes seen inside the aortic root represent the stent of the porcine valve. The cusps have a box like appearance in systole. In diastole a single linear echo is seen. The broad vertical arrow points to the posterior aortic wall. The thin vertical arrow to the left of it points to the stent. C = cusp, LV = left ventricle, RV = right ventricle.

obtain clear stent and aortic wall echoes free of secondary reverberations the reject setting of the Ekoline recorder had to be increased. The thickness of the stent and the aortic wall were measured when the reverberations were eliminated by high reject setting. The recording was made at 20 and 50 mm per second. Prosthetic mitral valves were visualized by tilting the transducer inferiorly and laterally in the direction of the left ventricle until the stent echoes were seen. Slight changes in transducer angulation enabled visualization of the cusps. It is noteworthy that unlike the experience with disc and ball prosthetic mitral valves transducer placement at the apex with medial and superior angulation was not useful in obtaining xenograft mitral valve echoes. The left ventricular outflow tract was measured from the anterior part of the stent to the inter ventricular septum.

## Results

**Porcine aortic valve.** The results are summarized in Table I.

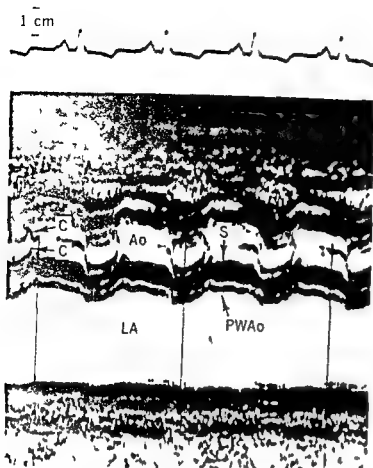
The stent of the porcine valve was represented by two parallel echoes within the aortic root which had the same pattern of motion as the aorta. These linear echoes were separated from

Table I Echocardiographic data of porcine xenograft valves in the aortic position

| Patient | Age | Sex | Valve size (cm) | Ao Stent (cm) | Inter cusp distance (cm) | Ao Stent ratio† |
|---------|-----|-----|-----------------|---------------|--------------------------|-----------------|
| 1       | 40  | M   | 2.1             | 0.01          | 0.7                      | 0.3             |
| 2       | 48  | M   | 2.7             | 0.5           | 1.1                      | 0.7             |
| 3       | 21  | M   | 2.7             | N‡            | 1.3                      | N               |
| 4       | 39  | M   | 2.3             | 0.4           | 1.2                      | 0.8             |
| 5       | 49  | M   | 2.7             | 0.3           | 1.1                      | 0.7             |
| 6       | 60  | F   | 2.1             | 0.3           | 1.3                      | 0.8             |
| 7       | 58  | M   | 2.5             | 0.3           | 1.5                      | 0.9             |
| 8       | 59  | M   | 3.1             | 0.3           | 1.6                      | N               |
| 9       | 16  | M   | 2.3             | 0.4           | 1.1                      | 0.8             |
| 10      | 50  | M   | 2.7             | 0.3           | 1.2                      | N               |
| 11      | 50  | M   | 2.3             | 0.3           | 1.1                      | 0.9             |
| 12      | 58  | M   | 2.7             | 0.3           | 1.1                      | 0.9             |
| 13      | 52  | M   | 2.5             | 0.4           | 1.1                      | 0.8             |
| 14      | 53  | M   | 2.7             | 0.4           | 1.5                      | 0.8             |
| Mean‡   |     |     |                 | 0.34          | 1.23                     | 0.8             |
| SD      |     |     |                 | 0.07          | 0.17                     | 0.07            |
| Range   |     |     |                 | 0.3-0.5       | 1.1-1.5                  | 0.7-0.9         |

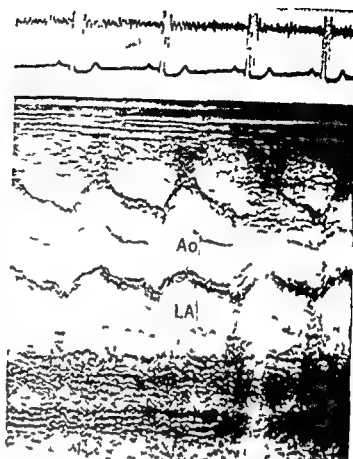
Ao-Stent = distance between aortic root and stent  
†Ao-Stent ratio = ratio of thickness of aortic wall to thickness of stent  
‡N = technically not suitable for accurate measurement

§The mean values do not include data from patients No. 1 and 3 with malfunctioning aortic valves  
||SD = standard deviation



**Fig 2** Echocardiogram of porcine valve in the aortic position from a patient who died 10 days later and whose autopsy showed extensive clot formation on the valve. The posterior stent echo is markedly thickened (8 mm). The space between the posterior stent echo and the aortic root is markedly diminished and no space is demonstrable in systole. The intercusp distance is diminished (7 mm). The anterior cusp is thickened. C = cusp PWAo = posterior wall aortic root S = stent

the anterior and posterior wall of the aortic root respectively (in the patients who were clinically improved after valve replacement) by a distance ranging from 3 mm to 5 mm mean was 3.3 mm. The cusps of the porcine aortic valve had a characteristic box like appearance in systole similar to that of the normal valve. An anterior and posterior cusp which opened briskly in systole and coapted in diastole were seen. In diastole, a single linear echo was present. The distance between the cusps in the patients who were clinically improved ranged from 1.1 to 1.5 cm mean was  $1.2 \text{ cm} \pm 0.15$  ( $\pm$  standard deviation). A sweep from the aortic root to the left ventricle is illustrated in Fig 1. The two parallel echoes within the aortic root represent the stent. The cusps of the porcine valve form a box like configuration in systole similar to that of the normal



**Fig 3** Preoperative echocardiogram of a patient who developed postoperative bacterial endocarditis. The maximum aortic root internal dimension is 3.7 cm. Ao = aortic root LA = left atrium

aortic valve. A single linear echo is seen in diastole. The ratio of the thickness of the aortic wall to that of the upright part of the stent ranged from 0.7 to 0.9 mean was 0.8.

The echocardiogram of the patient who had thrombus formation on the valve is illustrated in Fig 2. The aortic root echoes are thin. The space between the posterior stent echo and the posterior aortic root is markedly diminished and no space is demonstrable in systole. The posterior stent echo is markedly thickened (8 mm) and the ratio of the thickness of the aortic wall to that of the stent is decreased (0.3) compared to the other subjects. The intercusp distance is diminished (7 mm) when compared with patients with normally functioning valves. The anterior cusp is thickened. Another notable abnormality was that the cusp echoes were unusually prominent and were easily visible at high reject settings in contrast to the other subjects in whom a low reject setting was invariably required for adequate visualization of the cusps.

The preoperative echocardiogram of the patient who developed postoperative endocarditis

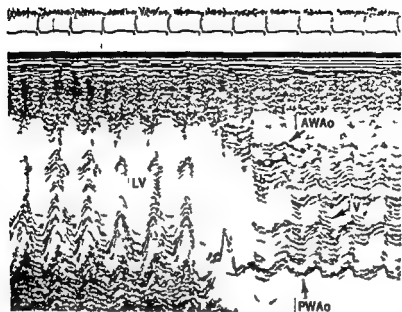


Fig 4 Echocardiogram of the patient referred to in Fig 3 taken after the development of infective endocarditis shows marked dilatation of the aortic root (6.3 cm). There are multiple diastolic echoes in the region of the valve cusps which may represent vegetations (V) on the cusps. AWAO = anterior wall of aortic root. PWAO = posterior wall of aortic root. LV = left ventricle.

is shown in Fig 3. The aortic root dimension is 3.7 cm. When compared with the preoperative record, the tracing taken after the development of infective endocarditis (Fig 4) shows marked dilatation of the aortic root (6.3 cm). There are multiple echoes in the region of the valve cusps in diastole which could represent vegetations on the valve.

**Porcine mitral valve.** Fig 5 shows a sweep from the aortic root to the left ventricle in a patient with a porcine mitral valve. The stent is represented by two parallel lines within the left ventricle. Two cusps which open in diastole and coapt in systole are visible. A single linear echo is seen in systole. Another example of a porcine mitral valve is shown on Fig 6. The cusps separate in diastole to form a box like appearance. A linear echo is seen between the anterior and posterior cusps. This could represent the third cusp of the porcine xenograft. The distance between the cusps ranged from 1.2 to 1.5 cm, mean was  $1.3 \text{ cm} \pm 0.13$ . The initial diastolic slope (EF slope) of the mitral valve ranged from 1.5 to 3.5 cm/second, mean =  $2.34 \pm 0.71$  (these values were obtained by averaging five beats).

#### Discussion

The porcine xenograft valve is similar to the human aortic valve in structure and function. Fig

7 shows a photograph of a normal porcine valve. The valve is mounted on a stent which has three upright parts which give rise to the parallel echoes seen on the echocardiogram. The porcine aortic valve consists of three cusps which open in systole giving rise to a box like appearance and coapt in diastole resulting in a single linear echo. Thus the echocardiographic appearance of the porcine valve closely resembles that of the normal aortic valve. The distance between the cusps however is less than that observed in a group of normal subjects studied in our laboratory. In the patients with normally functioning porcine valves the intercusp distance ranged from 1.1 cm to 1.5 cm, mean was  $1.2 \text{ cm} \pm 0.15$ , whereas in normal subjects the intercusp distance ranged from 1.5 cm to 2.4 cm with a mean of 1.8 cm. These data suggest that aortic valve orifice of the porcine valve is smaller than that of the normal human aortic valve. A recent report by Morris and associates<sup>1</sup> pointed out that there was an average peak systolic gradient of 23 mm Hg at rest and 37 mm Hg during exercise across porcine aortic valves. The calculated valve area<sup>1</sup> ranged from 0.75 to 1.67 square centimeters. Their results are consonant with our finding of smaller cusp excursion in the porcine valve group.

The two patients who developed clinically significant valvular dysfunction had abnormal

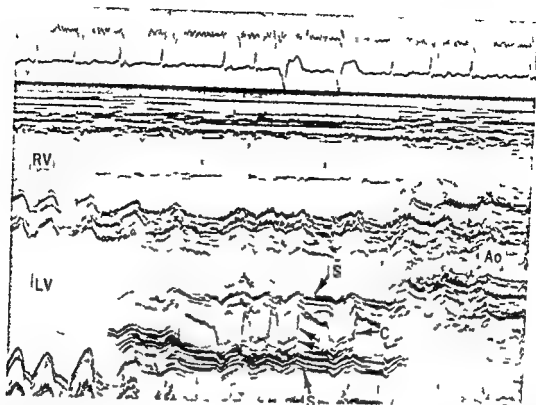


Fig 5 Echocardiogram which shows a sweep from the aortic root (Ao) to the left ventricle in a patient who had porcine valve replacement of the mitral valve. The stent is represented by two parallel lines within the left ventricle (LV). The cusps (C) open in diastole and coapt in systole producing a single linear echo. RV = right ventricle. S = stent.

Table II Ultrasound measurements of xenograft valves in the mitral position

| Patient | Age | Sex | Valve size (cm) | Inter cusp distance (cm) | LVOT*   |         | Valvar diastolic slope (cm/sec) | Septal motion |
|---------|-----|-----|-----------------|--------------------------|---------|---------|---------------------------------|---------------|
|         |     |     |                 |                          | ED (cm) | ES (cm) |                                 |               |
| 1       | 48  | M   | 31              | 12                       | 27      | 24      | 19                              | P             |
| 2       | 38  | F   | 25              | 15                       | 18      | 18      | 15                              | P             |
| 3       | 51  | F   | 25              | 13                       | 30      | 20      | 23                              | N             |
| 4       | 58  | F   | 23              | 12                       | 16      | 13      | 19                              | P             |
| 5       | 24  | F   | 27              | 13                       | 13      | 10      | 35                              | P             |
| 6       | 60  | F   | 23              | 12                       | 15      | 14      | 15                              | P             |
| 7       | 59  | M   | 31              | 15                       | 16      | 12      | 30                              | P             |
| 8       | 16  | F   | 29              | 12                       | 10      | 08      | 30                              | P             |
| 9       | 60  | F   | 27              | 12                       | 22      | 20      | 25                              | P             |
| Mean    |     |     |                 | 13                       | 19      | 154     | 234                             |               |
| SD      |     |     |                 | 0.13                     | 0.66    | 0.53    | 0.71                            |               |
| Range   |     |     |                 | 12-15                    | 10-30   | 08-24   | 15-35                           |               |

Abbreviations: LVOT = left ventricular outflow tract; ED = end diastole; ES = end systole; P = paradoxical; N = normal.

echocardiograms. Extensive clot formation on the valve was noted at autopsy on the first patient. The posterior part of the stent was markedly thickened, the distance between the posterior stent and the posterior aortic root was markedly reduced, the intercusp distance was reduced, the cusp echoes were unusually prominent and the anterior cusp was thickened. The postoperative course on the second patient was complicated by bacterial endocarditis affecting the porcine valve

and formation of a mycotic aneurysm of the aortic root. Dense echoes were noted in diastole in the region of the porcine valve. These could have represented vegetations on the valve. A striking change in aortic root diameter when compared with the preoperative dimension indicated the recent development of an aneurysm. The formation of a mycotic aneurysm of the aortic root is an unusual, but ominous complication of prosthetic valve endocarditis. Serial echo

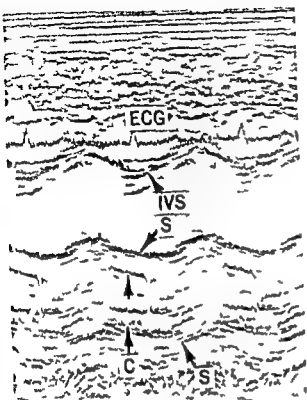


Fig 6 Echocardiogram of a patient who had porcine valve replacement of the mitral valve. The stent is represented by two parallel lines inside which are the cusps (C). The cusps open in diastole producing a box like configuration. A third linear echo is seen between the anterior and posterior cusp (arrow) which may represent a third cusp. The cusps coapt in systole producing a linear echo. S = stent. IVS = interventricular septum.

cardiography of the aortic root in patients with infective endocarditis may prove to be of value in the early detection of this serious complication. The above example points to the usefulness of a baseline ultrasound tracing in patients with prosthetic porcine valves. If a technically satisfactory tracing is obtained shortly after valve replacement, the development of a complication such as infective endocarditis, clot formation on the valve or aneurysm formation can be made with a much greater degree of confidence than if a baseline tracing was not available.

Porcine aortic xenograft replacement of the mitral valve results in a tricuspid left atrioventricular valve. The echocardiographic appearance of this valve was similar to that of the porcine aortic valve. Two parallel lines which represented the stent were seen within the left ventricle. An anterior and posterior cusp which produced a box like appearance in diastole were seen. The

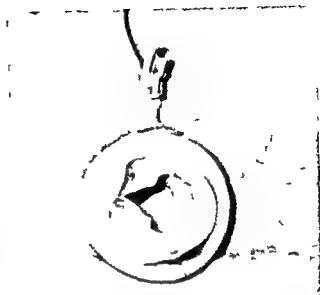


Fig 7 Photograph of a normal porcine xenograft valve. The stent has a base and three upright projections. The three cusps of the valve are seen in the open position.

coaptation of the cusps in systole resulted in a single linear echo. The intercusp distance ranged from 1.2 to 1.5 cm, mean was 1.3 cm. This distance is considerably less than that found in a group of normal subjects studied in our laboratory (intercusp distance ranged from 2.8 to 3.2 cm, mean was 3.0 cm). These data suggest that the orifice of the porcine valve in the mitral position is smaller than that of the human mitral valve. Our thesis is supported by the report of Johnson and associates<sup>12</sup> who found diastolic gradients across the mitral valve in all fourteen patients who were catheterized following mitral valve replacement with a porcine xenograft. The calculated valve area ranged from 0.92 cm<sup>2</sup> to 3.39 cm<sup>2</sup> and the average was 2.15 cm<sup>2</sup>.<sup>12</sup> It is interesting that unlike the normal mitral valve, the porcine mitral valve had a reduced EF slope. Thus some morphological changes such as flattening of the EF slope which are used in diagnosing stenosis of the normal mitral valve will be of limited value in diagnosing porcine valve stenosis. In a recent report Horowitz and associates<sup>13</sup> described calcific homograft stenosis which was characterized by increased echo density from the tissue leaflets and thrombus formation on the sewing ring which was associated with decreased leaflet excursion and decreased ratio of internal to external stent diameter.<sup>13</sup> Horowitz and associates also studied a group of patients with



normally functioning bio prosthetic valves in the mitral position. The dimensions for the left ventricular outflow tract that they obtained were similar to those seen in our patients. The inter cusp distance in their group was slightly greater than the figures obtained in our study. This was probably because the prosthetic valve size was in general smaller in our group of patients.

In summary the echocardiographic features of the mitral and aortic porcine xenograft valve are presented. Two patients developed serious complications. Both had abnormal echocardiograms. Echocardiography may prove to be a useful tool in the follow up of patients with porcine valves and in the detection of early prosthetic malfunction.

### Summary

Echocardiograms were performed on 33 prosthetic porcine valves. Satisfactory tracings of the valve were obtained in 23 (70 per cent). The characteristic appearance of the porcine aortic prosthesis consisted of two lines parallel to each other within the aortic root, which had the same pattern of motion as the aortic root. These lines probably represented the stent of the porcine valve. The valve cusps had a characteristic box-like appearance in systole similar to that of the normal aortic valve. A single echo was seen in diastole. The distance between the cusps in systole in patients who were clinically improved after valve replacement ranged from 1.1 cm to 1.5 cm with a mean of 1.2 cm. This distance is less than that observed in a group of normal subjects studied in our laboratory range 1.5 to 2.4 cm mean 1.8 cm. Two patients developed clinically significant valvular dysfunction. The first patient had dense echoes on the anterior cusp and the stent and reduced intercusp distance. He died ten days later and extensive thrombus formation on the porcine valve was noted. The second patient developed infective endocarditis of the porcine valve and a mycotic aneurysm of the aorta. Multiple diastolic echoes were seen in the region of the porcine valve and marked enlargement of the aortic root (6.3 cm) when compared with the preoperative record (3.7 cm) was noted.

The stent of the porcine mitral valve was represented by two parallel echoes in the left ventricular cavity. The valve cusps had a box-like

configuration in diastole similar to the normal aortic valve. The distance between the cusps ranged from 1.2 cm to 1.5 cm mean was 1.3 cm.

Unlike the normal mitral valve motion of the valve in diastole was flat and the characteristic M shaped complex was not present. In summary, echocardiography may prove to be a useful tool in the assessment of the normal and malfunctioning prosthetic porcine xenograft valves.

### REFERENCES

- 1 Hildner F J. Detection of prosthetic valve dysfunction by bedside and laboratory evaluation. *Cardiovasc Clin* 5: 289 1973.
- 2 Ben Zvi J, Hildner F J, Chandraratna P A N and Samet P. Thrombosis on Bjork Shiley aortic valve prosthesis. *Am J Cardiol* 34: 538 1974.
- 3 Hylan J C, Kloster F E, Herr R H, Hull F Q, Ames A W, Starr A and Grswold H E. Phonocardiographic diagnosis of aortic ball valvane. *Circulation* 38: 90 1968.
- 4 Colin L H and Collins J J. Elimination of the need for anticoagulation following mitral valve replacement. *Am J Cardiol* 35: 128 1975.
- 5 Cohn L H, Lamberti J J, Castaneda A, Collins J J. Cardiac valve replacement with the glutaraldehyde stabilized porcine aortic valve. Indications, operative results and follow up. *Chest* 66: 321 1974.
- 6 Johnson M L, Paton B C and Homes J H. Ultrasonic evaluation of prosthetic valve motion. *Circulation* 42: 113 1970.
- 7 Oliva P E, Johnson M L, Pomerantz M and Levene A. Dysfunction of the Beall mitral prosthesis and its detection by cinefluoroscopy and echocardiography. *Am J Cardiol* 31: 393 1973.
- 8 Gibson T C, Starek P J K, Moos S and Craige E. Echocardiographic and phonocardiographic characteristics of the Lillehei Kaster mitral valve prosthesis. *Circulation* 49: 434 1974.
- 9 Chandraratna P A N, Lopez J M, Hildner F J, Samet P and Ben Zvi J. Diagnosis of Bjork Shiley aortic valve dysfunction by echocardiography. *Am J Heart J* 91: 318 1976.
- 10 Horowitz M S, Tecklenberg P L, Goodman D J, Harrison D C and Popp R L. Echocardiographic evaluation of the stent mounted aortic bioprosthetic valve in the mitral position. In vitro and in vivo studies. *Circulation* 54: 91 1976.
- 11 Morris D C, Wickliffe C W, King S H, Douglas J S and Jones E L. Hemodynamic evaluation of the porcine xenograft aortic valve. *Am J Cardiol* 37: 157 1976.
- 12 Johnson A, DiDonna G, Peterson K, LeWinter M, Blair M and Daily P. Functional evaluation of the porcine heterograft valve in the mitral position. *Abstr Circulation* 50: 111 42 1974.
- 13 Horowitz M S, Goodman D J, Hancock E W and Popp R L. Noninvasive diagnosis of complications of the mitral bioprosthesis. *J Thorac Cardiovasc Surg* 71: 450 1976.

# Arrhythmias and the 'Holiday Heart' Alcohol-associated cardiac rhythm disorders

Philip O Ettlinger MD  
Chia F Wu MD  
Catalino De La Cruz Jr MD  
Allen B Weiss MD  
S Sultan Ahmed MD  
Timothy J Regan MD  
Newark and Englewood N J

An association between alcohol use and cardiac arrhythmias particularly atrial fibrillation has long been suspected.<sup>1</sup> However the specific etiologic role of alcohol is difficult to establish and indeed doubt may exist as to the presence of any heart disease when overt cardiomyopathy is not present. Recent observations in our laboratory and by others have indicated that acute and chronic alcohol ingestion leads to demonstrable depression of myocardial function in animals and man,<sup>2</sup> and that cardiac conduction abnormalities and morphologic changes may result as well.<sup>3</sup>

Between January 1972 and January 1976 we observed or reviewed 37 separate dysrhythmic episodes requiring hospitalization in 24 patients who drank heavily and habitually with superimposition of especially heavy ingestion prior to the arrhythmia. Overt alcoholic cardiomyopathy was not present; the group was selected only insofar as all patients drank heavily had arrhythmias and had normal or borderline heart size (by x ray).

From the Department of Medicine, College of Medicine and Dentistry of New Jersey-New Jersey Medical School and Martin H. Opatul U. of New Jersey and the Englewood Hospital, Englewood, New Jersey.

This research was supported in part by Research Grant No. AA00 42 from the National Institute of Alcohol Abuse and Alcoholism and Postgraduate Training Grant No. HL 05510 from the National Heart and Lung Institute and Research Grant No. 75-BER 1 from the Bergen County Heart Association, New Jersey Affiliate-American Heart Association.

Received for publication November 22, 1976

Accepted for publication January 5, 1977

Reprint requests: Philip O. Ettlinger MD CMDN1-New Jersey Medical School, 100 Bergen St., Newark, N. J. 07103

and normal or borderline ECGs after return to sinus rhythm. The clinical and physiological characteristics of these patients, the spectrum of their arrhythmias and treatment and the unusual temporal distribution of the arrhythmias form the basis of this report.

## Methods

All but one patient were seen at two hospitals visited by one of us (P. O. E.). At Martland Hospital the major teaching hospital of the New Jersey Medical School at Newark, N. J. serving an economically depressed area 18 patients (25 admissions) were evaluated. At Englewood Hospital Englewood, N. J., a community hospital located in a prosperous suburban region five patients (five admissions) were observed. One typical patient admitted to another local hospital and later studied by us was included and a prior alcohol-associated arrhythmia in a distant hospital by another patient is also included. Most patients were seen in referral from other physicians at the two hospitals; no attempt was made to survey retrospectively all hospital admissions for arrhythmias as a connection between alcohol ingestion and rhythm disturbance was rarely made prior to consultation with us. All patients seen by us during this period who satisfied the criteria of alcohol-associated arrhythmia, normal ECG and chest x-ray and no clinical evidence of heart disease were included.

Arrhythmias were the reason for admission in 30 instances; manifested by palpitations, precordial pressure, sharp left chest pain or passing

out spells History was often sketchy Two patients came to the hospital with fibular fractures consequent to being injured while intoxicated Neither had head or chest injuries, nor was a history of trauma obtained from any other patient

Initial ECG and chest x rays were obtained in all and ECGs were repeated daily Arterial and venous blood was taken on admission for arterial gases, pH, CBC, electrolytes, LDH urea, glucose cholesterol, and SGOT Blood alcohol was measured in eight patients Treatment was at the discretion of the admitting physician, all patients survived Later, the day of the week on which each admission occurred as well as the monthly distribution was analyzed statistically The latter was compared with monthly hospital totals for other, traditionally accepted alcohol associated illnesses (including delirium tremens acute and chronic alcoholism, alcoholic psychosis, episodic and habitual drinking alcoholic addiction, and Laennec's cirrhosis) obtained by review of hospital discharge diagnoses between January, 1971, and December, 1974

To exclude overt cardiomyopathy or other cardiovascular disorders, only patients without x ray evidence of cardiac enlargement and with normal or borderline ECG after return to normal rhythm were included No patient had angina, history of rheumatic fever or murmur, myocardial infarction, peripheral vascular disease, diabetes or hyperlipidemia One was moderately obese None had any murmur extra heart sound, or apical thrust on physical examination One had mild chronic hypertension (BP 160/90) in several the admitting blood pressure was elevated but returned quickly to normal A qualitative and quantitative history of alcohol use was obtained by intensive questioning of each patient and where available other family members Later we attempted to evaluate all patients further although several signed out of the hospital early or failed to return for scheduled studies

Systolic time interval measurements (prejection period [PEP] left ventricular ejection time [LVET] and their ratio [PEP/LVET]) were made in the postabsorptive state in 17 of the 24 patients at least three days after return to sinus rhythm All medication had been stopped at least 48 hours earlier The systolic time intervals were measured using the method and instrumentation

described by Weissler and colleagues " " simultaneously recorded ECG's, phonocardiograms, and carotid pulse tracings recorded photographically at paper speeds of 150 or 200 mm/sec with time markers at 0.02 sec Ten complexes were measured for each subject Total electromechanical systole (Q S) and left ventricular ejection time (LVET) were measured directly and the PEP was calculated by subtraction  $([Q S] - [LVET])$  The ratio PEP/LVET was derived for each patient and a mean ratio was calculated for the group, the mean PEP/LVET ratio was compared with that of 17 normal age matched subjects Because of heart rate differences corrected values for PEP (PEPI) and LVET (LVETI) in milliseconds were obtained using the following regression formulas  $PEPI = PEP \text{ (measured)} + 0.40 \times HR$  for women,  $PEPI = PEP \text{ (measured)} + 0.41 \times HR$  for men,  $LVETI = LVET \text{ (measured)} + 1.6 \times HR$ , for women,  $LVETI = LVET \text{ (measured)} + 1.7 \times HR$  for men

High speed (200 mm/sec) high frequency (0.1 to 2000 Hz) recordings of standard ECG limb leads were obtained at the same time Heart rate PR interval, QRS duration, and QT intervals were each measured in the three leads and the longest duration of each was taken at the true duration PR and QT were corrected for rate by dividing each by the square root of the preceding RR interval A group of ten age and sex matched normal persons without arrhythmia or drinking history were studied during the same period for comparison

In order to rule out significant coronary artery disease and evaluate left ventricular performance eleven patients were studied by diagnostic right and left heart catheterization at intervals of one to four months following the dysrhythmic episodes Intracardiac pressure data recordings, cardiac outputs by dye-dilution left ventriculography, selective coronary arteriography and His bundle electrography were performed in all In eight patients an additional catheter was placed in the aortic root so that dye-dilution measurement of left ventricular volume and ejection fraction could be obtained by injecting indocyanine green dye into the left ventricle and sampling from the aortic root using methods previously reported " Five patients had duplicate measurements of left ventricular end diastolic pressure and stroke index at rest and then during

intravenous infusion of a dilute solution of angiotensin. For the latter measurements were made during the tenth to twentieth minutes following elevation of the aortic diastolic pressure by about 15 to 20 mm Hg. In all cases hemodynamic measurements were completed prior to or at least 45 minutes after angiography. Hemodynamic data in the alcoholic subjects was compared with that obtained in a selected group of 12 normal persons studied in our laboratory: eight normals underwent angiotensin testing.

Comparisons between alcoholic and normal groups were made utilizing Student's *t* test for unpaired mean data. Chi square analysis was used in the evaluation of admitting day making the assumption that Sunday through Tuesday admissions should have been only 3/7 of the total.

### Illustrative cases

**Case 1 J McC** a 69 year old doorman lived alone and drank heavily. During December 1971 he received many bottles of liquor from the tenants of the apartment house where he worked. He worked on New Year's Eve but drank upon returning home: he fell asleep but awoke with precordial pressure and palpitations and at 2 A.M. on January 1, 1972 was brought to the hospital emergency room. Atrial fibrillation with a rapid ventricular response was seen. K was 2.7 mEq/L. Treatment with digoxin was begun and the rhythm converted to RSR. He was lost to follow up after discharge.

**Case 2 D H** a 33 year old business man spent a long weekend drinking heavily in a motel. After three days he developed palpitations and on Tuesday September 30, 1969 he was seen at another hospital with atrial fibrillation and was cardioverted. He felt well but gradually resumed consumption of 12 to 15 cans of beer daily. Four years later on Wednesday October 10, 1973 he presented at the hospital emergency room with palpitations. Frequent atrial extrasystoles (with LBBB aberration) were treated with quinidine. Plasma electrolytes were normal. Since reducing his beer consumption and continuing quinidine palpitations have lessened although he has frequent palpitations when he drinks more heavily.

**Case 3 M H** a 31 year old woman drank whiskey in quart quantities daily. On Thursday December 27, 1973 she was seen at the hospital emergency room because of palpitations and breathlessness. atrial fibrillation with ventricular extrasystoles was present. Within minutes the rate accelerated with runs of beats of uncertain origin possibly ventricular tachycardia. Cardioversion was performed immediately. Plasma electrolytes were normal. In the next two years she was admitted on three additional occasions, each time with atrial fibrillation and the same drinking history. One each occurred on a Sunday, Monday, and Tuesday.

**Case 4 W K** a 43 year-old businessman consumed at least six oz. of martinis daily for many years. During December 1974 he had additional liquor at business luncheons. On Monday December 30, 1974 he "passed out" while seated in a cinema and was taken to the hospital emergency room.

Frequent ventricular extrasystoles were present and the plasma K was 2.7 mEq/L. Treatment with procainamide and K suppressed the arrhythmia. Three weeks later while asymptomatic and arrhythmia free at rest an exercise stress test induced ventricular extrasystoles and runs of ventricular tachycardia after the exercise and thus arrhythmia was presumed to be the basis of his presenting symptoms. With abstinence and outpatient treatment with quinidine the arrhythmia has not recurred.

### Results

**Clinical data** Twenty patients in our series were male and four female (aged 25 to 62 years mean 43 years). All but three were between 30 and 60 years old: eight patients were in the fourth decade, seven in the fifth and six in the sixth decade. All gave histories of consuming at least 6 to 10 drinks daily. A history of at least ten years of heavy ethanol consumption was usually present as a background. All varieties of beer and whiskey were implicated alone or in combination. Most patients drank every day of the week but indicated that weekend consumption was higher. We have not yet observed this disorder in anyone who drank wine alone although this may be a cultural difference inasmuch as wine drinkers are less frequent in our population than whiskey or beer drinkers. All but two patients smoked heavily.

Following resolution of the arrhythmias most patients were asymptomatic although one developed overt alcoholic hepatitis and two had delirium tremens. None of these three were further studied. Low plasma potassium previously implicated as a possible cause of arrhythmias in alcoholics and of arrhythmias and conduction disturbances in general was less than 3.5 mEq/L in only four of 30 instances although a whole body potassium deficit was not excluded. SGOT was usually normal or borderline elevated. Blood alcohol determinations were performed on admission in eight patients and were positive in six ranging from 50 to 430 mg per cent. Plasma sodium chloride bicarbonate lactic dehydrogenase urea sugar and cholesterol were normal. Arterial blood gases and pH were normal in all. Plasma magnesium was not measured.

Fig 1 indicates the admitting day of the week in each instance. Nineteen patients were initially seen between Sunday and Tuesday with Monday admissions most common. By chi square testing 19 of 32 episodes occurring on three of the seven days of the week is significantly greater than the

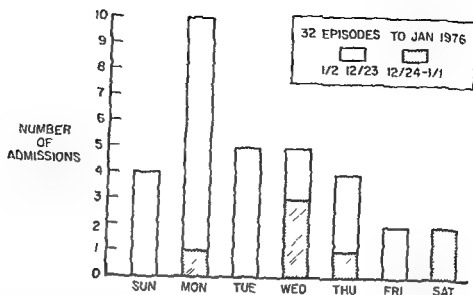


Fig 1 Admitting day for alcoholic arrhythmias. Nineteen admissions were seen Sunday through Tuesday (post weekend). Of the 13 Wednesday through Saturday admissions, six were during the year end holidays. Therefore 25 of 32 admissions were holiday related.

Table I ECG and chest x rays in Holiday Heart patients

|   |    |
|---|----|
| Electrocardiograms (total 24)   |    |
| Fully normal  | 16 |
| Normal except LAD -10 to -30  | 4  |
| Normal except P wave 0.12 sec   | 2  |
| T waves low (not flat) 12 leads (one of these also showed first degree A-V block) | 2  |
| Chest roentgenograms (total 24)   |    |
| Fully normal  | 21 |
| Cardiothoracic ratio 50%  | 3  |

Table II Alcohol associated arrhythmias\*

| Rhythm abnormality            | No                           |
|-------------------------------|------------------------------|
| Isolated APCs                 | 4                            |
| Atrial fibrillation           | 12                           |
| Atrial flutter                | 6                            |
| Paroxysmal atrial tachycardia | 3                            |
| Junctional tachycardia†       | 4 (3 in 1 patient)           |
| Isolated PVCs                 | 6                            |
| Ventricular tachycardia       | 1 (after treadmill exercise) |

\*Several patients had more than one arrhythmia. Of atrial arrhythmias 6 showed RBBB and 3 LBBB aberration.  
†One patient with junctional tachycardia showed atrioventricular dissociation.

3/7 expected,  $P < 0.05$ . Further examination of the data is even more striking, as six of the 13 admissions from Wednesday through Saturday were seen between December 24 and January 1. If these six holiday admissions are added to the 19 post weekend admissions, then fully 25 of the 32

episodes could truly be considered examples of a holiday heart syndrome—a name which has been used at our institutions to describe them.

In Fig 2, the number of alcoholic arrhythmia admissions per month over the four year period is shown. Only two patients were seen between May and August while the incidence peaked in December and January. In the bottom graph the mean combined monthly incidence of hospital admissions for all other traditionally accepted alcohol associated illnesses are tabulated for comparison in three years of the four year period. These other illnesses did not fall into any seasonal pattern.

**Electrocardiographic and x ray data.** ECGs in 16 patients were fully normal after resolution of arrhythmia (Table I) whereas four showed mild left axis deviation (up to -30 degrees), two were normal except for a broad P wave and two had minimal T wave abnormalities. Many had transitory post conversion ECG abnormalities with evidence of atrial and/or ventricular extrasystoles, ST-T abnormalities and QT prolongation but the tracings returned to normal within 48 hours. Some patients were observed to show diminutive or absent Q waves in ECG Leads I and V<sub>6</sub> (absent septal Q)—a finding previously reported to be common in cardiomyopathy.<sup>14</sup> However these were not possible to compare quantitatively with normals because of differences in technical quality of the electrocardiograms which were examined retrospectively.

Routine chest x rays indicated normal cardiac

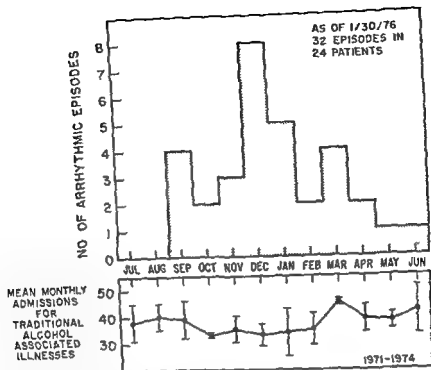


Fig 2 Monthly distribution of holiday heart hospital admissions (top) compared with mean monthly admissions for traditional alcohol associated illnesses (bottom). The apparent year end peak of alcoholic arrhythmias is not present for the "traditional" alcoholic illnesses.

size in 21 (cardiothoracic ratio  $< 50$  per cent normal appearing silhouette). The cardiothoracic ratio was 50 per cent in three patients.

**Arrhythmias observed.** The most commonly seen arrhythmia was atrial fibrillation followed by atrial flutter and isolated ventricular premature beats (Table II). The latter were especially common in association with atrial fibrillation when the ventricular rate was rapid. Several patients each had isolated multiple supraventricular beats and paroxysmal atrial tachycardia. Four episodes of junctional tachycardia were observed—three in one patient and a fourth associated with transient atrioventricular dissociation in another person. During arrhythmias six instances of right bundle branch block type aberration and three of the left bundle branch block type were observed, but several of these occurred at rapid ventricular rates. Consequently it was not possible to describe aberration quantitatively although it was present unexpectedly in some patients at relatively slow rates.

**Medical treatment of arrhythmias.** Treatment of all patients was usually begun in the emergency room; no protocol was followed. Dioxin was used most commonly, although cardiover-

sion pressor infusions, quinidine, procainamide and carotid massage were all employed. Eight episodes went untreated and resolved spontaneously. All patients survived.

**Systolic time intervals.** The mean PEP/LVET ratio in the alcoholics  $0.412 \pm 0.014$  was significantly different from that obtained in the age matched controls  $0.299 \pm 0.008$ ,  $P < 0.001$  (Fig 3). The measured mean PEP was longer and the mean LVET shorter in the alcoholics. Because of heart rate differences (the mean heart rate of the alcoholics during systolic time interval testing was  $82 \pm 3$  BPM and of normals  $67 \pm 2$  BPM,  $P < 0.001$ ), PEP alone and LVET alone were not directly comparable. However, when corrected for heart rate (PEPI and LVEI), the mean PEPI was indeed longer ( $136 \pm 3$  msec in alcoholics,  $116 \pm 3$  msec in controls,  $P < 0.001$ ) and mean LVEI shorter ( $383 \pm 7$  msec in alcoholics,  $407 \pm 3$  msec in controls,  $P < 0.005$ ) in the alcoholic group.

**High speed electrocardiographic data.** Results of high speed electrocardiographic measurements of PRC, QRS duration and QTc are shown in Table III. The mean for alcoholic patients measured 17 per cent higher for PRC, 23 per cent

P &lt; 0.001

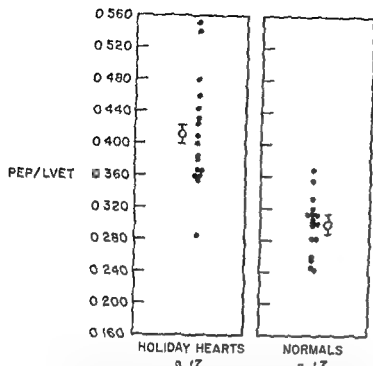


Fig 3 Systolic time interval ratios (PEP/LVET) in patients with arrhythmias (left) and in normals (right) Filled circles are individual data points means are open circles and standard errors are shown

higher for QRS, and 14 per cent higher for QTc in comparison with normals

**Cardiac catheterization data** Mean cardiac index was significantly lower in the alcoholic group ( $2.6 \pm 0.2$ , normals  $3.3 \pm 0.2$  L/minute  $P < 0.05$ ). However other measurements including mean left ventricular end diastolic pressure and volume indices mean stroke volume index mean end systolic volume index mean ejection fraction, and mean velocity of contractile element shortening did not differ significantly from normal. Nevertheless four patients had left ventricular end diastolic pressures in excess of 12 mm Hg (up to 20 mm Hg) and in all data categories the mean differences from normal varied in a direction consistent with abnormality (The mean heart rate at the time of study in our catheterized normal group was 80 BPM while in the alcoholic group it was 67 BPM thus accounting for a low mean cardiac index in the alcoholics with a normal mean stroke volume index).

During the angiotensin infusions aortic diastolic pressure rose 17 mm Hg in the alcoholic group and 21 mm Hg in normals. Left ventricular end diastolic pressure rose significantly and equivalently (alcoholics  $80 \pm 13$  to  $120 \pm 23$  mm Hg normals  $63 \pm 0.6$  to  $100 \pm 0.5$  mm Hg) in both

Table III P QRS T durations from high speed ECG

|                  | Holiday Hearts (N = 17) | Normals (N = 10) | P         |
|------------------|-------------------------|------------------|-----------|
| PRc (msec)       | $179 \pm 7$             | $153 \pm 6$      | $< 0.01$  |
| QRS (msec)       | $98 \pm 3$              | $80 \pm 2$       | $< 0.001$ |
| QTc (msec)       | $430 \pm 9$             | $377 \pm 6$      | $< 0.001$ |
| Heart rate (BPM) | $82 \pm 3$              | $63 \pm 3$       | $< 0.001$ |

One patient had first degree A-V block and is excluded from PRc measurements

groups and the mean values in both states were not significantly different in the two groups. Stroke volume index, however, did not change in the alcoholics ( $38.5 \pm 2.3$  to  $36.1 \pm 1.4$  ml/beat/ $M^2$ ), while in the normal group it rose significantly ( $38.4 \pm 2.9$  to  $45.5 \pm 3.1$  ml/beat/ $M^2$ ,  $P < 0.02$  for intergroup comparison). The inability to increase stroke volume with rising end diastolic pressure is considered further evidence of left ventricular dysfunction.

Selective coronary arteriograms and left ventriculograms were normal in all 11 patients studied, the mean H-V time,  $42 \pm 2$  msec, was normal as well.

### Discussion

The 24 patients included in this study each gave a similar history of prolonged heavy alcohol use with recent superimposition of more intensive weekend or holiday drinking. Cardiac arrhythmias developing in these circumstances are in our experience, often misdiagnosed as idiopathic, as no clinical evidence of heart disease remains after resolution of the rhythm problem and the extent of alcohol use may be unrecognized. Because of the rather typical weekend or holiday presentation we have called this the holiday heart syndrome, which we define as an acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing without evident residual with abstinence. Our report details numerous atrial and ventricular arrhythmias and one instance of transitory atrioventricular block. The unusual seasonal peak at year end and early in the New Year corresponds to the known peak of liquor sales at that time.<sup>19</sup>

While the year end and the post weekend

tendency toward arrhythmias is clear in these heavy drinking patients it is not clear why similar disturbances are not seen in proximity to the July 4 and Labor Day holidays. Dilution of the alcohol during the summer with other liquids may prevent rapid absorption thus preventing excessive blood levels from developing.

The mechanism by which these arrhythmias occur is not known. Conduction and rhythm disturbances are common in overt alcoholic cardiomyopathy<sup>1</sup>; bundle branch block, atrioventricular block, atrial and ventricular arrhythmias have all been reported. Alcoholic excess may be accompanied by malnutrition and effects of malnutrition or associated coronary artery disease or electrolyte disturbances have been difficult to exclude. In recent investigations from our laboratory chronic conduction abnormalities including H V and QRS prolongation were induced in otherwise healthy and well nourished dogs that drank ethyl alcohol in quantity for longer than one year.<sup>1</sup> In these animals infiltration of the myocardial interstitium with Alcian Blue positive material and electron microscopic evidence of intercalated disc disruption were observed either of which alteration could have been responsible for prolonged conduction. Cardiac hypertrophy was not present. Cardiac conduction delays are believed to play an important role in arrhythmia production by facilitating reentry.<sup>1</sup> While the PR, QRS and QT prolongations observed in the current series of patients are modest it is possible that more severe localized areas of delay are present. Indeed histologic evaluation of the heart in human cardiomyopathy and after alcoholic ingestion by animals emphasize a variable patchy distribution of lesions.

The acute effects of alcohol on the ECG are only seen with serum levels above 600 mg/100 ml or more. Respiratory arrest with hypoxia may predispose to arrhythmias under these conditions.<sup>1</sup> We have previously shown that isolated ventricular ectopic beats may occur only 1½ to 2½ hours after the onset of moderate alcohol administration however. Ethanol shortens atrial muscle refractory period<sup>1</sup> which might induce atrial arrhythmias but the serum alcohol concentrations required are much higher than those observed in alcoholic man. The patients we studied were usually seen during or immediately after a drinking episode. Some of the arrhythmias

actually began at a time of intoxication although some patients recalled onset of palpitations as an abrupt event occurring when they were not intoxicated. Nevertheless the odor of ethanol was apparent at the time of admission in many and serum alcohol levels were elevated in most cases in which they were obtained. While the outcome in our patients was benign the very rapid rates observed in several suggested that the result might not have been salutary outside the hospital. Such arrhythmias might be a cause of the sudden death commonly reported in alcoholics.<sup>11</sup>

Evidence for mild left ventricular dysfunction in this group was not unexpected. As early as 1969 reports from this laboratory and others showed that preclinical cardiac dysfunction in apparently noncardiac chronic alcoholics could be demonstrated.<sup>11-13</sup> We believe that a preclinical cardiomyopathy is present in the majority of these patients. Although we have not yet observed the transition to overt cardiomyopathy in any patient perhaps because of the limited period follow up in at least three patients a diagnosis of a possible cardiomyopathy might be entertained because of borderline cardiomegaly.

While this report deals specifically with arrhythmias occurring in chronic drinkers it appears that alcohol is occasionally able to precipitate similar disturbances in persons who do not admit to habitual alcohol use. We observed one episode of atrial fibrillation (on New Year's Eve) in a 52 year old otherwise healthy woman who insisted that she had taken only one cocktail a few hours earlier. Too little data is available now regarding this particular subgroup but it deserves further study.

### Summary

An association between excessive alcohol use and cardiac rhythm disorders is often difficult to establish in the absence of overt cardiomyopathy. We studied 32 separate hospital admissions for dysrhythmias in 24 patients (20 men, 4 women) with heavy recent alcohol ingestion and prolonged excessive alcohol use. None had evidence of overt heart disease after treatment of arrhythmia. Episodes usually followed heavy weekend or holiday spree resulting in hospitalization between Sunday and Tuesday or in proximity to the year end holidays, a relationship not observed in other alcohol associated illnesses. Atrial fibril-



lation was most common, but atrial flutter atrial tachycardia junctional tachycardia multiple APCs, multiple PVC's and ventricular tachycardia were also observed. Transient hypokalemia was present in four of 30. The mean PEP/LVET ratio after treatment was  $0.412 \pm 0.014$  (normal  $0.299 \pm 0.008$ ,  $P < 0.001$ ). High speed ECGs showed prolongation of PRc, QRS and QTc. At cardiac catheterization intracardiac pressures and volumes coronary arteriograms and ventricular wall motion were normal at rest and mean cardiac index was slightly low, but the left ventricular response to angiotensin was abnormal. Cardiac arrhythmias presenting during weekend or holiday drinking episodes are associated with conduction delays and depressed cardiac performance indicative of early cardiomyopathy and suggest a holiday heart syndrome.

We gratefully acknowledge the secretarial services rendered by Mrs A Binetti Mrs A Brown and Mrs M Pittman. Drs L Strom S Frier and J Kam allowed us to see and report their patients. The technical assistance of Mr J Fiore Mr M Feuerman and Mrs D Dolan RN and the guidance of Dr G E Levinson are also appreciated. Drs S Patrawalla and B Haider assisted with cardiac catheterization. Ms M Hayes Record Room Librarian at Martland Hospital compiled the data on alcohol related admissions.

## REFERENCES

- Evans W. The electrocardiogram of alcoholic cardiomyopathy. *Br Heart J* 21:445 1959
- Bridgen W and Robinson J. Alcoholic heart disease. *Br Med J* 2:1283 1964
- Bellet S. Clinical disorders of the heart beat third edition. Philadelphia 1971. Lea and Febiger pp 175-207
- Regan T J, Khan M I, Ettinger P O et al. Myocardial function and lipid metabolism in the chronic alcoholic animal. *J Clin Invest* 54:740 1974
- Regan T J, Weiss A B, Moschos C B et al. The myocardial effects of acute and chronic usage of ethanol in man. *Trans Assoc Am Physicians* 78:282 1965
- Regan T J, Korotvedis G, Moschos C B et al. The acute metabolic and hemodynamic responses of the left ventricle to ethanol. *J Clin Invest* 45:270 1966
- Ahmed S S, Levinson G E, and Regan T J. Depression of myocardial contractility with low doses of ethanol in normal man. *Circulation* 48:378 1973
- Gould L, Zahur M, DeMartino A et al. Cardiac effects of a cocktail. *JAMA* 218:1790 1971
- Spodick D H, Pigott V M, and Churif N. Preclinical cardiac malfunction in chronic alcoholism. *N Engl J Med* 287:677 1972
- Burch G E, Colcolough H L, Harb J M et al. The effects of ingestion of ethyl alcohol wine and beer on the myocardium of mice. *Am J Cardiol* 27:522 1971
- Ettinger P O, Lyons M M, Oldewurtel H A et al. Cardiac conduction abnormalities produced by chronic alcoholism. *Am Heart J* 91:65 1976
- Weissler A M, Harris W W, and Schoenfeld C D. Bedside techniques for the evaluation of ventricular function in man. *Am J Cardiol* 23:577 1969
- Ahmed S S, Levinson G E, Schwartz C J et al. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 46:559 1972
- Levinson G E, Frank M J, Nadimi M et al. Studies of cardiopulmonary blood volume. Measurement of left ventricular volume by dye dilution. *Circulation* 35:1038 1967
- Ross J Jr and Braunwald E. The study of left ventricular function in man by increasing resistance of ventricular ejection with angiotensin. *Circulation* 29:739 1964
- Vetter W R, Cohn L H, and Reichgott M. Hypokalemia and electrocardiographic abnormalities during acute alcohol withdrawal. *Arch Intern Med* 120:536 1967
- Davidson S and Surawicz H. Ectopic beats and atrioventricular conduction disturbances in patients with hypokalemia. *Arch Intern Med* 120:280 1967
- Flowers N C and Horan L C. Electrocardiographic and vectorcardiographic features of myocardial disease in The myocardial disease edited by N O Fowler. New York and London 1973. Grune & Stratton Inc p 184
- Simon S S and Costigan R. Personal communication (Privileged data of State of New Jersey Department of Treasury Division of Taxation)
- Leier C V, Schaaf S F, Leighton R F et al. Heart block in alcoholic cardiomyopathy. *Arch Intern Med* 134:766 1974
- Ettinger P O, Regan T J, Oldewurtel H A et al. Ventricular conduction delay and arrhythmias during regional hyperkalemia in the dog. *Circ Res* 33:521 1973
- Hibbs R G, Ferrans V J, Black W C et al. Alcoholic cardiomyopathy. An electron microscopic study. *Am Heart J* 69:766 1965
- Alexander C S. Idiopathic heart disease II. Electron microscopic examination of myocardial biopsy specimens in alcoholic heart disease. *Am J Med* 41:229 1966
- Wakum H G. The effects of ethyl alcohol on the isolated heart. *Fed Proc* 5:109 1946
- Loomis T A. The effect of alcohol on myocardial and respiratory function. *Q J Stud Alcohol* 13:561 1952
- Haggard H W, Greenberg L A, Cohen L H, et al. Studies on the absorption, distribution and elimination of alcohol IX. The concentration of alcohol in the blood causing primary cardiac failure. *J Pharmacol Exp Ther* 71:358 1941
- Gimeno A L, Gimeno M D, and Webb J L. Effects of ethanol on cellular membrane potentials and contractility of isolated rat atrium. *Am J Physiol* 203:194 1962
- Kramer K, Kuller L, and Fisher R. The increasing mortality attributed to cirrhosis and fatty liver in Baltimore (1957-1966). *Ann Intern Med* 71:273 1968
- Regan T J, Levinson G E, Oldewurtel H A et al. Ventricular function in noncardiacs with alcoholic fatty liver. Role of ethanol in the production of cardiomyopathy. *J Clin Invest* 48:397 1969
- Wu C F, Sudhakar M, Jafari G et al. Preclinical cardiomyopathy in chronic alcoholics. A sex difference. *Am Heart J* 91:281 1976

# Angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries A clinicopathologic study of 9 patients with progressive systemic sclerosis

Bernadine H Bulkley MD  
Peter G Klacsmann MD  
Grover M Hutchins MD  
Baltimore Md

Generally ischemic heart disease can be ascribed to lesions of the epicardial coronary arteries.<sup>1</sup> Although uncommon the occurrence of angina pectoris myocardial ischemia and necrosis and/or sudden cardiac death with angiographically normal coronary arteries has been the subject of considerable interest and speculation<sup>2,3</sup> but autopsy documentation of this entity is generally lacking and its etiology remains obscure. Kemp and associates<sup>4</sup> have suggested the possibility of regional functional arterial or arteriolar constriction but without supporting evidence.

It has been recognized for many years that progressive systemic sclerosis (PSS) may be associated with myocardial fibrosis and in 1943 Weiss and colleagues<sup>5</sup> noted the peculiarity of myocardial scars in patients without associated coronary artery disease. The functional significance of the myocardial lesion in PSS as well as its etiology however have been the subject of controversy. It has been suggested that the fibrosis in the heart as well as elsewhere in the body in PSS is due to abnormal collagen proliferation<sup>6,7</sup> and some have claimed that the myocardial abnormalities

are mainly secondary to severe renal and pulmonary disease.<sup>17</sup> Another possible explanation is that an underlying vasomotor abnormality accounts for systemic hypertension and renal disease,<sup>8</sup> pulmonary hypertension<sup>9</sup> and the myocardial disease<sup>10</sup> of PSS.

This report describes ischemic myocardial disease associated with angina pectoris, arrhythmias, myocardial necrosis and/or sudden death in nine patients with morphologically normal coronary arteries who had progressive systemic sclerosis and Raynaud's phenomenon. The pattern of necrosis in these patients suggests a myocardial Raynaud's phenomenon as one possible pathophysiologic mechanism of ischemic heart disease with morphologically normal coronary arteries.

## Methods

We recently studied morphologic features of the myocardial disease associated with PSS in the first 52 patients with this disease autopsied at The Johns Hopkins Hospital and found that an unexplained myocardial lesion was present in approximately half of them.<sup>18</sup> Since that time three additional patients have been studied including a 12 year old child who died of a myocardial infarct with morphologically normal coronary arteries. The striking clinical presentation of acute myocardial infarction and sudden death in a young girl led us to review the other patients with progressive systemic sclerosis who had clinical evidence of ischemic heart disease but morphologically normal coronary arteries.

From the Cardiovascular Division of the Department of Medicine and the Department of Pathology, The Johns Hopkins Medical Institution, Baltimore, Md.

Supported by Grants F-01 HL-16550-01 with The National Institutes of Health, Public Health Service Department of Health Education and Welfare and the Stehle Research Foundation.

Received for publication Dec 29, 1976.

Accepted for publication Feb 10, 1977.

Reprint requests to Dr. Bernadine H. Bulkley, Cardiovascular Division, The Johns Hopkins Hospital, Baltimore, Md. 21205.

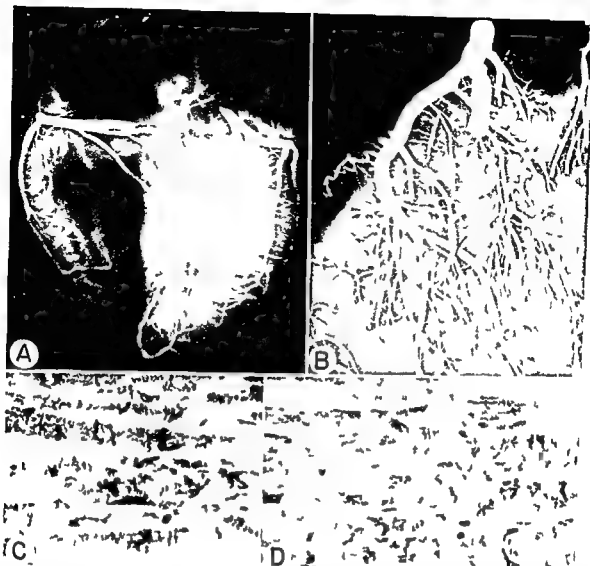


Fig 1 Postmortem angiogram (A) and microangiogram (B) of the heart of a 12 year old girl (Case No 1) who died during an episode of Raynaud's phenomenon. Epicardial and intramural coronary arteries were widely patent by angiography and light microscopy. C Extensive necrosis of the contraction band type was present throughout right and left ventricles as shown in this photomicrograph from a central portion of a focal lesion in the left ventricle. D Margin of another focal lesion with unaffected muscle cells at upper left. (B original magnification  $\times 74$ ; C and D phosphotungstic acid hematoxylin stain original magnifications  $\times 600$  and  $\times 500$ .)

Of 55 autopsied patients with progressive systemic sclerosis 50 had widely patent coronary arteries. Of this latter group nine had clinical and pathologic evidence of ischemic myocardial disease including angina pectoris, myocardial necrosis and sudden cardiac death but morphologically normal coronary arteries. Sudden death was defined as death within six hours of onset of symptoms. These nine patients form the subject of this report.

Clinical and autopsy records were reviewed in each of the nine patients. In each patient gross specimens of heart were reexamined and histologic sections of lung, kidney, upper and lower gastrointestinal tract, skeletal muscle and skin were examined. In addition a minimum of 5 and

an average of 50 histologic sections of myocardium were examined from each heart. Epicardial coronary arteries from each patient were examined by multiple transverse sections at approximately 5 millimeter intervals in the nine patients and in addition by barium sulfate postmortem angiography in one (Case No 1). In the latter case microangiograms were prepared from tissue blocks of both ventricles and examined by light microscopy (Fig 1) to assess the microvasculature.

## Results

**Clinical observations.** The nine patients ranged in age from 12 to 70 years (average 44 years) and six were women. In eight patients the diagnosis of

PSS was made during life by skin and/or esophageal abnormalities. In one patient (Case No. 1) the 12 year old girl non specific muscular complaints and progressively severe Raynaud's phenomenon were present for 18 months before death but the diagnosis of PSS was not made until autopsy. Clinically severe restrictive lung disease had been present in two patients (Cases No. 6 and 9) for several years. Renal dysfunction was evident in only one patient (Case No. 7) and in her led to acute renal failure and death. Two of the nine patients (Cases No. 4 and 5) had systemic hypertension. In all nine patients Raynaud's phenomenon was present and in two patients (Cases No. 1 and 9) was of increasing severity over several days immediately prior to their sudden death. Chest pains of unknown cause were present in six patients and in three the diagnosis of angina pectoris was made and confirmed by an exercise stress test or ischemic ST-T wave changes on electrocardiogram during pain. None of the patients underwent cardiac catheterization. Electrocardiograms were abnormal in all nine patients showing non specific ST-T wave changes in five right bundle branch block (associated with pulmonary PSS) in two premature ventricular contractions in six including ventricular bigeminy in three and runs of ventricular tachycardia in one. In two patients a 54 year old woman (Case No. 9) and the 12 year old girl (Case No. 1) transient ST segment elevations were noted during an episode of chest pain at rest in the former and immediately prior to death in the latter. Ischemic ST changes, arrhythmias and/or chest pains shortly before death led to the clinical impression that sudden death was due to an acute myocardial infarction in four patients (Cases No. 1, 2, 3 and 8). In four others with a history of multiple premature ventricular contractions sudden death was thought to be related to the ventricular arrhythmias (Cases No. 4, 5, 6 and 9). One patient with a history of well documented angina pectoris died of renal failure, sepsis and congestive heart failure. Since a seasonal relationship to mortality in PSS has been observed the time of year that each patient died was reviewed and is indicated in Table I. Of the eight patients dying suddenly four died in the fall or winter months and four in June or July. The other patient died of renal failure in July.

**Autopsy findings.** At autopsy the diagnosis of PSS was confirmed by typical PSS changes in the

skin and gastrointestinal tract, lung and/or kidney in all nine patients. Sclerodermatous parenchymal disease was severe in the lung in two patients and in the kidney in one (Case No. 7). With the exception of the latter case the most striking abnormalities were present in the heart and in eight of the nine patients appeared to be the only cause of death.

The hearts weighed from 250 to 475 Gm and three exceeded 350 Gm. The extramural coronary arteries were widely patent in each patient. In eight of the nine patients the intramural coronary arteries were morphologically normal on multiple histologic sections and by microangiogram in one (Fig. 1). In one patient (Case No. 2) focal thickening of approximately 10 per cent of the small vessels examined was observed and occasional thrombi were present within their lumens.

The myocardium in all patients showed a similar lesion consisting of extensive focal fibrosis involving both right and left ventricle. Focal areas of acute and subacute necrosis were also present in seven of the nine hearts and in each contraction bands were present within myocardial cells in focally necrotic zones of myocardium. The areas of myocardial fibrosis and necrosis were not limited to the distribution of a particular extramural coronary artery but were randomly demonstrated throughout the myocardium from epicardium to endocardium and were present in both right and left ventricles. In the 12 year old patient (Case No. 1) who died during an episode of Raynaud's phenomenon contraction band necrosis was most striking and involved an estimated 30 per cent of myocardium (Fig. 1). In none of the eight patients dying suddenly were other explanations for their sudden death evident at autopsy.

## Discussion

This report describes nine autopsied patients who had clinical histories characteristic of ischemic heart disease during life and myocardial necrosis and fibrosis at autopsy but widely patent coronary arteries. Chest pain had been present in six of them during life and in three transient ischemic ST-T wave changes were documented during episodes of pain. Unexplained ventricular arrhythmias were also a feature of this group of patients. Causes other than coronary disease were not available for most of these patients to account for their cardiovascular

Table 1 Patients studied

| Case age/sex        | General clinical findings   | Cardiovascular findings  | Autopsy findings   |
|---------------------|---|--|--|
| <b>Sudden death</b> |   |  |  |
| 1<br>12 F           | Raynauds 1 yr fatigue leg cramps periorbital edema elevated CPK suspected functional illness Died in September  | Normotensive after 3 days of severe Raynauds had unexpected cardiopulmonary arrest associated with ST elevation V <sub>2</sub> V <sub>3</sub> diagnosed as acute anterior MI   | PSS lesions of skin esophagus kidney lungs Heart-normal IMCA EMCA 4+ focal CB necrosis subacute necrosis and 2+ focal fibrous scarring                                 |
| 2<br>38 M           | Raynauds 1 yr fatigue darkening skin severe muscle weakness exertional dyspnea mild dysphagia mild restrictive lung disease weight loss Died in September                         | Normotensive mild CHF ECG—poor R wave progression suggestive of remote MI dull aching substernal chest pain 24 hours PTD unexplained complete heart block SD   | Severe PSS lesions esophagus stomach colon mild pulmonary renal Heart-normal EMCA focal thickening and thrombi in IMCA severe (3+) focal fibrosis and CB necrosis (3+) |
| 3<br>40 F           | Tenosynovitis 4 yrs dermatitis dysphagia with abnormal esophageal duodenal and jejunal motility No pulmonary or renal dysfunction Died in July                                    | Normotensive history of pericarditis recurrent anterior chest pain unknown etiology 6 weeks before death unexplained arrhythmias persisting over 10 days PTD including multifocal PVCs with bigeminy acute MI suspected SD | Mild PSS lesions esophagus skin lung no renal disease Heart-normal EMCA IMCA extensive focal CB necrosis (4+) with inflammation focal fibrosis (2+)                    |
| 4<br>40 F           | Raynauds 3 yrs fatigue weight loss edema of hands and feet dysphagia diarrhea No renal or pulmonary dysfunction Died in July  | Systemic hypertension intermittent precordial chest pain of unknown etiology dyspnea on exertion ECG—normal 3 days PTD had PAC PVC SD  | Mild PSS lesions esophagus skin kidney no pulmonary lesions Heart-normal EMCA IMCA focal moderate (2+3) fibrosis and necrosis with contraction bands                   |
| 5<br>50 M           | Raynauds 2½ yrs digital ulcers increased skin pigmentation and tightening muscle weakness abnormal esophageal and small bowel motility no renal or pulmonary disease Died in June | Mild systemic hypertension (160/90) PVCs 9 months PTD unexplained CHF 2 months PTD improved on digitalis and diuretics SD  | Severe PSS lesions esophagus mild lesions skin lung Heart-normal IMCA EMCA severe focal necrosis with contraction bands (4+) and focal fibrosis (3+)                   |
| 6<br>70 F           | Raynauds 20 yrs Skin thickening arthralgias restrictive lung disease (VC 75% predicted) recurrent bronchitis dysphagia Died in July   | Normotensive CHF 2 years before death intermittent chest pain not relieved by nitroglycerin ECG—RBBB multifocal PVCs with bigeminy SD  | Severe PSS lesions esophagus lung skin no renal disease Heart-normal EMCA IMCA moderate to severe focal scarring (3+) and focal necrosis (3+) with contraction bands   |

Abbreviations CB = contraction bands CHF = congestive heart failure CPK = creatine phosphokinase ECG = electrocardiogram EMCA = extramural coronary arteries IMCA = intramural coronary arteries MI = myocardial infarction PAC = premature atrial contractions PSS = progressive systemic sclerosis PTD = prior to death PVC = premature ventricular contractions RBBB = right bundle branch block bD = sudden death VC = vital capacity yr = year  
Grades of histologic injury 1+ trace 2+ mild 3+ moderate 4+ marked

dysfunction. In six of the nine renal and pulmonary disease were mild or absent. Only two patients had systemic hypertension and none had valvular heart disease.

Sudden unexpected death occurred in eight of these nine patients (although in one patient sudden death was associated with worsening heart failure) and was presumed to be due to arrhythmias or myocardial infarction in all of them. That sudden death was cardiac in origin was confirmed by autopsy. Severe myocardial lesions were present, and no other cause of death

was evident. Perhaps most striking, however, was the finding of acute myocardial necrosis compatible with their clinical signs of ischemic heart disease but widely patent extramural coronary arteries and morphologically normal intramural coronary arteries.

A clue to the pathophysiology of the seemingly ischemic heart disease with normal coronary arteries was present, however, in the type of myocardial damage. Contraction band necrosis was present in seven patients. Contraction band necrosis is a form of myocardial cell injury which

Table 1 Cont d

| Case age/sex  | General clinical findings   | Cardiovascular findings   | Autopsy findings  |
|---|---|---|---|
| <i>Angina pectoris with or without sudden death</i> |   |   |   |
| 7<br>45 F   | Raynauds 2 yrs arthralgias tightening of skin of hands face chest dysphagia no pulmonary disease acute renal failure and sepsis leading to death over 10 day period Died in July  | Normotensive palpitations and substernal chest pain for 2 years positive Masters test congestive heart failure 1 month PTD  | Mild to moderate PSS lesions esophagus small bowel lung severe renal disease Heart-normal EMCA IMCA severe focal scarring (4+) no necrosis fibrinous pericarditis                             |
| 8<br>40 M   | Raynauds 1 yr arthralgias mild dysphagia skin tightening over hands no pulmonary or renal problems. Died in February  | Normotensive angina pectoris for 5 years with ST segment depression during pain CHF 1 year PTD ECG-left axis deviation PVC bigeminy rapidly progressive CHF with SD   | Mild PSS lesions esophagus skin lung no renal disease Heart-normal EMCA IMCA marked focal scarring (3+) no necrosis   |
| 9<br>54 F   | Raynauds 16 years dysphagia 6 years severe restrictive lung disease (VC 21% predicted) normal renal function marked increase in Raynauds over 3 weeks PTD leading to cold blue fingers by time of death purple with early trophic changes Died in January | Normotensive intermittent precordial chest pain 1 month PTD severe chest pain at rest associated with ST elevation V V with subsequent inversion of T waves V V for several days ECG RBBB PVC SD at home 10 days after hospital discharge | Moderate to severe PSS lesions esophagus, lung no renal disease Heart-normal EMCA IMCA Severe focal scarring (4+) and focal acute necrosis (3+) with contraction bands and acute inflammation |

may be distinguished from the commonly recognized form of ischemic damage coagulation necrosis. Coagulation necrosis can be produced experimentally by permanent occlusion of a coronary artery. Contraction band necrosis less frequently seen and only recently recognized as a distinctive lesion differs morphologically from coagulation necrosis by the presence of dense eosinophilic transverse contraction bands<sup>20-22</sup>. Experimental and clinical studies have led to the recognition of contraction band necrosis as a reperfusion lesion. The lesion is frequently present in patients after cardiac surgery performed with cardiopulmonary bypass<sup>23</sup> and may be produced experimentally by temporary coronary artery occlusion followed by reperfusion. That contraction band necrosis is a reperfusion lesion and was present in seven of our patients and in seven of the eight who died suddenly suggests that their myocardial damage was a consequence of transient nonperfusion.

One possible explanation for transient nonperfusion of myocardium in these patients is recurrent spontaneous ventricular tachycardia or fibrillation. For myocardial damage to result from an episode of spontaneous ventricular fibrillation the period of nonperfusion would have to

be longer than several minutes however and none of these patients gave a history of syncope lapse of consciousness or previous cardiac arrest.

Another possible explanation would be spasm or Raynaud's phenomenon of the coronary arteries. Transient nonperfusion or Raynaud's phenomenon of the digits and kidneys<sup>14</sup> and possibly the lungs is a recognized feature of PSS and likely accounts for many of the morphologic changes observed in these organs. It is similarly likely that the myocardial damage is due to a Raynaud's phenomenon of the intramyocardial arteries of the heart. Intermittent vascular spasm at some level of the microcirculation would also account for the contraction band type of necrosis. Such injury would be cumulative and would explain both the necrosis and fibrosis present in these patients and its presence throughout both right and left ventricle. Coronary angiography in one patient with PSS myocardial disease has been reported<sup>1</sup> and in that patient the extramural coronary arteries were normal but there was unusually slow clearance of contrast material from the coronary vessels suggesting increased resistance of the capillary bed due to some abnormality of the

microcirculation. Since we found no consistent morphologic abnormalities in the small coronary vessels of 52 patients (20) with PSS including eight of the nine described here, it is most likely that the abnormality is functional rather than structural.

That epicardial coronary arterial spasm can last long enough to cause not only myocardial ischemia but also infarction has been demonstrated angiographically in patients with patent coronary arteries.<sup>8-6</sup> Engel and colleagues<sup>20</sup> recently described a patient with myocardial infarction resulting from angiographically documented spasm of the right coronary artery and otherwise normal coronary arteries who had a possible Raynaud's phenomenon of the hands and feet during episodes of chest pain.

In our nine patients with PSS a Raynaud's phenomenon of the heart would explain angina pectoris, ventricular arrhythmias and sudden death. Transient ischemic changes in electrocardiograms in three patients during angina and the preterminal electrocardiographic evidence of transmural ischemia in the 12 year old girl all in the setting of morphologically normal coronary arteries supports the notion of some type of intermittent spasm. Two patients died suddenly after several days of severe persistent Raynaud's phenomenon of the fingers. Contraction band necrosis was most prominent in both of their hearts. Although the temporal relationship between Raynaud's phenomenon of the digits and a similar phenomenon in the lungs, kidneys or heart is not necessary, Cannon and associates<sup>19</sup> using Xe<sup>133</sup> washout techniques and renal arteriography, demonstrated reductions in renal cortical blood flow in a few patients with PSS when Raynaud's phenomenon of the hands was induced by cold water immersion.

Cannon and associates<sup>19</sup> also performed a seasonal analysis of deaths in their patients with PSS and showed that among 40 patients three fourths of all deaths caused by malignant hypertension and renal failure occurred in the fall and winter months. They suggested that sudden transition from warm to cold climate may have been analogous to 'cold immersion'. A similar analysis of our patients with cardiac PSS failed to show such a striking seasonal relationship to mortality. Half of our patients with sudden cardiac death died in the fall or winter months and this included the two patients dying during episodes of

Raynaud's phenomenon. The other half of the sudden death group, however, died in June or July and it was impossible to determine whether these patients were subject to sudden temperature changes such as those associated with exposure to air conditioning.

There has been considerable interest in the mechanism of angina pectoris and myocardial infarction in the setting of normal coronary arteries by angiography. It is likely that many processes may account for this condition, and proposed mechanisms have included coronary arterial embolism and lysis, extramural arterial spasm, abnormalities and lactate metabolism and abnormalities of oxyhemoglobin dissociation.<sup>2-10</sup> Nonetheless, evidence for these mechanisms is sparse, autopsy confirmation of the myocardial lesion and the coronary arterial patency infrequent and the existence of the condition as a single pathophysiologic entity is controversial. These nine patients with PSS represent one of the largest autopsy series of angina pectoris, and/or myocardial infarction with normal coronary arteries. In them a pathophysiologic mechanism, episodic spasm of intra-myocardial vessels, seems to be one explanation for their clinical and pathological features. As such, the patients with PSS, and what may be a myocardial Raynaud's phenomenon, form a possible model for one form of angina or infarction with normal coronary arteries.

### Summary

The syndrome of angina pectoris or acute myocardial infarction without obstructive coronary artery disease has been the subject of much interest. We studied nine autopsied patients with progressive systemic sclerosis and evidence of ischemic heart disease but morphologically normal coronary arteries. Three patients had angina pectoris and three others chest pains of unknown etiology, six had ventricular arrhythmias, four had clinically suspected acute myocardial infarction and eight had sudden cardiac death. At autopsy, extensive focal myocardial necrosis was present in seven patients and myocardial scarring in all nine, but all patients had widely patent intramural and extramural coronary arteries. The finding of contraction band myocardial necrosis in seven of the eight patients who experienced sudden death suggests that the myocardial damage was a consequence of

reperfusion of focally nonperfused myocardium and thus due to a myocardial Raynaud's phenomenon. Patients with PSS may provide a model of spasm of intramyocardial vessels causing angina pectoris or myocardial infarction with morphologically normal coronary arteries.

We would like to thank Mrs Enka L. Bohanan, Miss Sue A. Leatherwood and Mrs. Joanna A. Walton for their expert assistance.

## REFERENCES

- Ridolfi R L and Hutchins G M. The relationship between coronary lesions and myocardial infarction. Ulceration of atherosclerotic plaques precipitating coronary thrombosis. *Am HEART J* 88: 468 1977.
- Prouffit W L, Shurey E K and Sones F M. Selective cine coronary arteriography. Correlation with clinical findings in 1000 patients. *Circulation* 33: 901 1966.
- Likoff W, Segal B L and Kaspasian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 276: 1063 1967.
- Neill W A, Kassebaum D G and Judkins M P. Myocardial hypoxia as the basis for angina pectoris in a patient with normal coronary arteriograms. *N Engl J Med* 279: 789 1968.
- Ebott D L and Bratt G. The paradox of myocardial ischemia and necrosis in young women with normal coronary arteriograms. Relation to abnormal hemoglobin-oxygen dissociation. *Am J Cardiol* 23: 633 1968.
- Dear H D, Russell H O, Jones W B et al. Myocardial infarction in the absence of coronary occlusion. *Am J Cardiol* 28: 718 1971.
- Likoff W. Myocardial infarction in subjects with normal coronary arteriograms. *Am J Cardiol* 28: 147 1971.
- Bruchke A V G, Bruynel K J J, Bloch A et al. Acute myocardial infarction without obstruction coronary artery disease demonstrated by selective cinearteriography. *Br Heart J* 33: 587 1971.
- Clancy D L, Marcus M L and Epstein S E. Myocardial infarction in young women with normal coronary arteriograms. *Circulation* 44: 425 1971.
- Neill W A, Judkins M P, Dhindsa D S et al. Clinically suspect ischemic heart disease not corroborated by demonstrable coronary artery disease. Physiologic investigations and clinical course. *Am J Cardiol* 29: 1 1972.
- Ebott D L, Baroldi G and Leone A. Necropsy studies in myocardial infarction with minimal or no coronary luminal reduction due to atherosclerosis. *Circulation* 49: 1127 1974.
- Kemp H G, Elliott W C and Gorlin R. The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 80: 59 1967.
- Kemp H G, Vokonas P S, Cohn P F and Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 54: 135 1973.
- Weiss S, Stead E A Jr, Warren J V, et al. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. *Arch Intern Med* 71: 749 1943.
- Oram S and Stokes W. The heart in scleroderma. *Br Heart J* 23: 743 1961.
- Sackner M A, Heinz E R and Steinberg A J. The heart in scleroderma. *Am J Cardiol* 17: 549 1966.
- D'Angelo W A, Fries J F, Mast A T et al. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med* 48: 4 1969.
- Sokoloff L. Some aspects of the pathology of collagen diseases. *Bull N Y Acad Med* 32: 760 1966.
- Cannon P J, Hassar M, Case D B et al. The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. *Medicine* 53: 1 1974.
- Bulkley B H, Ridolfi R L, Salyer W H et al. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. *Circulation* 48: 483 1973.
- Herdson P B, Sommers H M and Jennings R B A comparative study of the fine structure of normal and ischemic dog myocardium with special reference to early changes following temporary occlusion of a coronary artery. *Am J Pathol* 46: 367 1966.
- Reichenbach D D and Benditt E P. Myofibrillar degeneration. A response of the myocardial cell to injury. *Arch Pathol* 85: 189 1968.
- Roberts W C, Bulkley B H and Morrow A G. Pathologic anatomy of cardiac valve replacement. A study of 221 necropsy patients. *Progr Cardiovasc Dis* 15: 339 1973.
- Gupta M P, Zonerach S, Zeitlin W et al. Scleroderma heart disease with slow flow velocity in coronary arteries. *Chest* 67: 116 1975.
- Cheng T O, Bashout T, Singh H H et al. Myocardial infarction in the absence of coronary atherosclerosis. Result of coronary spasm? (*?*) *Am J Cardiol* 30: 680 1972.
- Engel H J, Page H L Jr and Campbell W B. Coronary artery spasm as the cause of myocardial infarction during coronary arteriography. *Am HEART J* 91: 501 1976.



# Effect of coronary collaterals on left ventricular function at rest and during stress

Franz Schwarz M D  
Willem Flameng, M D  
Roland Ensslen M D  
Michael Sesto M D  
Jochen Thormann M D  
*Bad Nauheim West Germany*

During recent years there still exists controversy concerning the effectiveness of coronary collateral vessels in man as a compensatory mechanism for the loss of blood flow consequent to coronary obstruction.<sup>1-4</sup> In the dog heart rudimentary collateral vessels enlarge during gradual occlusion of a major coronary artery and perfuse the myocardium distal to complete occlusion to such an extent that only little or no myocardial damage results in this area provided the luminal narrowing was slow enough.<sup>5-7</sup> Pathologic and angiographic studies in man have also shown that severe coronary obstructions are not regularly associated with transmural myocardial infarction or scars if an adequate compensating collateral circulation exists.<sup>8-11</sup> Large differences in size and extent of collaterals can be shown by angiography and comparison of preoperative angiograms and intraoperative flow measurements indicate that radiographic appearance of coronary collateral circulation is related to the flow capacity of these vessels.<sup>12-14</sup> Furthermore normal flow in the area distal to complete coronary occlusion could be measured by radioisotope studies in several patients in whom cinearteriography revealed an adequate retrograde filling of the occluded artery.<sup>15-18</sup> Therefore the angiographic evaluation seems to be a reliable method to estimate collateral flow. The purpose of this study was to investigate the adequacy of coronary collaterals in the presence of complete coro-

nary occlusion by measuring total and regional left ventricular contractile function at rest and during stress. Clinical data were reviewed to compare coronary morphology and subjective complaints.

## Methods

A consecutive series of 169 patients having significant coronary artery disease (more than 75 per cent luminal obstruction of at least one major coronary artery) was studied. From this series all patients with complete occlusion of the proximal part of at least one of the three major coronary arteries were selected (87 patients). Additional coronary stenoses of less than 75 per cent luminal narrowing were present in a few patients and were not considered. Patients with atrial fibrillation, with valvular heart disease with severe disease of the main stem of the left coronary artery and patients with technically poor angiographies were excluded from the study.

Cardiac catheterization was performed without premedication in the fasting state. A biplane cineventriculogram (30 degree right anterior oblique position, 50 ml Renografin 36 frames per second using 35 mm films and six inch image intensifiers) was followed by coronary arteriography in the right and left anterior oblique positions using the Judkins technique. A pacing test was performed in a subgroup of 12 of 87 patients with complete occlusion of the descending branch of the left coronary artery. Six of these patients showed good collaterals and six showed poor collaterals (as defined below) to the occluded vessel. For this purpose a bipolar pacing electrode was placed into the apex of the right ventricle (19).

From the Kerckhoff Klinik Bad Nauheim West Germany

Received for publication Jan 11 1977

Accepted for publication Mar 4 1977

Reprint requests: F Schwarz M D Kerckhoff Klinik Beneke Strasse  
II 6350 Bad Nauheim West Germany



Fig 1A and B A Well collateralized occlusion of the anterior descending branch of the left coronary artery. Left coronary injection RAO projection early filling phase complete occlusion of the anterior descending branch (arrow) with retrograde filling over a large collateral vessel (arrowhead) originating from the patent marginal branch B Late filling phase uninterrupted filling of the distal segment and septal branches are seen

femoral vein) Thirty minutes after the last coronary arteriogram right ventricular pacing was started at a rate of 110 b p m and was gradually increased under left ventricular pressure registration to a rate of 180 b p m This rate was kept constant for one minute After stopping of pacing ventriculography was immediately repeated If pain occurred during this procedure nitroglycerin was given after ventriculography and pain was relieved in all cases where it was observed

The coronary occlusions of the anterior descending branch (LAD) the circumflex branch (LC) of the left coronary artery and the right coronary artery (RC) as well as the collateral circulation were analyzed from the cineangiograms and were tabulated

Radiographic criteria for the presence of collateral vessels were (a) retrograde filling of a major vessel after injection of contrast medium into another vessel or (b) filling of the distal segment of a proximal occluded major vessel after injection into the proximal stump of the same artery Collateralization was termed good if the distal segment of the occluded artery and its branches was visualized without interruption and if the average caliber of the distal segment measured greater than 1.0 mm after correction for the angiographic magnification When the distal segment was interrupted and/or the average

caliber was only 1.0 mm or less collateral circulation was considered poor Each case was evaluated including measurement of the distal segment by two observers In cases which showed two or three vessel occlusions good collateralization was accepted if each vessel fulfilled the criteria for good collaterals This classification of collaterals resembles that used by several investigators<sup>2-4</sup> but differs from that used by others<sup>5</sup> Examples of well collateralized occlusions are shown in Figs 1 and 2

Quantitative biplane ventriculography was performed using the area-length method<sup>6-7</sup> For calculation of segmental wall motion and LV volumes ectopic and postectopic cycles were eliminated The ventriculograms of 17 normal patients without heart disease (average age  $44.3 \pm 3.5$  years) served as controls Biplane ejection fraction was derived from the ratio of angiographic stroke volume to end diastolic volume times 100 per cent Segmental wall motion was quantitatively analyzed according to the technique of Herman and Gorlin<sup>8</sup> End diastolic and end systolic silhouettes were outlined from the 30 degree right anterior oblique projection The long axis (L) was drawn from the mid-aortic root to the apex and three equally spaced perpendiculars were constructed creating six hemiaxes from the long axis to the endocardial surface These axes

# Effect of coronary collaterals on left ventricular function at rest and during stress

Franz Schwarz M D  
Willem Flameng M D  
Roland Ensslen M D  
Michael Sesto, M D  
Jochen Thormann M D  
*Bad Nauheim West Germany*

During recent years there still exists controversy concerning the effectiveness of coronary collateral vessels in man as a compensatory mechanism for the loss of blood flow consequent to coronary obstruction.<sup>1-11</sup> In the dog heart rudimentary collateral vessels enlarge during gradual occlusion of a major coronary artery and perfuse the myocardium distal to complete occlusion to such an extent that only little or no myocardial damage results in this area provided the luminal narrowing was slow enough.<sup>12-14</sup> Pathologic and angiographic studies in man have also shown that severe coronary obstructions are not regularly associated with transmural myocardial infarction or scars if an adequate compensating collateral circulation exists.<sup>15-18</sup> Large differences in size and extent of collaterals can be shown by angiography and comparison of preoperative angiograms and intraoperative flow measurements indicate that radiographic appearance of coronary collateral circulation is related to the flow capacity of these vessels.<sup>19-21</sup> Furthermore, normal flow in the area distal to complete coronary occlusion could be measured by radioisotope studies in several patients in whom cinearteriography revealed an adequate retrograde filling of the occluded artery.<sup>22-24</sup> Therefore the angiographic evaluation seems to be a reliable method to estimate collateral flow. The purpose of this study was to investigate the adequacy of coronary collaterals in the presence of complete coronary

occlusion by measuring total and regional left ventricular contractile function at rest and during stress. Clinical data were reviewed to compare coronary morphology and subjective complaints.

## Methods

A consecutive series of 169 patients having significant coronary artery disease (more than 75 per cent luminal obstruction of at least one major coronary artery) was studied. From this series all patients with complete occlusion of the proximal part of at least one of the three major coronary arteries were selected (87 patients). Additional coronary stenoses of less than 75 per cent luminal narrowing were present in a few patients and were not considered. Patients with atrial fibrillation with valvular heart disease with severe disease of the main stem of the left coronary artery and patients with technically poor angiographies were excluded from the study.

Cardiac catheterization was performed without premedication in the fasting state. A biplane cineventriculogram (30 degree right anterior oblique position 50 ml Renografin 36 frames per second using 35 mm films and six inch image intensifiers) was followed by coronary arteriography in the right and left anterior oblique positions using the Judkins technique.<sup>25</sup> A pacing test was performed in a subgroup of 12 of 87 patients with complete occlusion of the descending branch of the left coronary artery. Six of these patients showed good collaterals and six showed poor collaterals (as defined below) to the occluded vessel. For this purpose a bipolar pacing electrode was placed into the apex of the right ventricle (Fig 1).

From the Kerckhoff Klinik Bad Nauheim West Germany

Received for publication Jan 11 1977

Accepted for publication Mar 4 1977

Reprint requests: F Schwarz M D Kerckhoff Klinik Beneke Strasse  
D 6340 Bad Nauheim West Germany

occlusions (10 patients). Isolated LC and two and three vessel occlusions were rarely found (Table I). The ejection fraction was significantly higher in well collateralized LAD occlusion and RC occlusion as compared to poorly collateralized occlusions of the same subgroup ( $p < 0.001$ ). Comparison with the average of normal individuals shows no significant difference ( $p > 0.05$ ) of ejection fraction in patients with well collateralized occlusion of LAD and occlusion of RC. In contrast poorly collateralized occlusions of LAD, RC, LAD + RC and RC + LC showed significantly depressed ejection fractions (all  $p < 0.001$ ). All other subgroups were too small for statistical comparisons.

The analysis of segmental wall motion is shown in Table II. In poorly collateralized LAD occlusion anterior wall motion ( $R$  to  $R_s$ ,  $L$ ) was significantly lower than in well collateralized LAD occlusion ( $p < 0.05$  respectively  $< 0.01$ ,  $p < 0.001$ ). The same was found in RC occlusion for inferior wall motion ( $R$  to  $R_s$ ). Comparison of normally contracting ventricles to well collateralized occlusions reveals slight hypokinesia of  $R$  and  $L$  in well collateralized LAD occlusion and normal motion in well collateralized RC occlusion ( $p > 0.05$ ). Severely reduced wall motion was found in poorly collateralized occlusions of the same areas ( $p < 0.01$  respectively  $p < 0.001$ ).

Table III presents mean values of anterior wall motion at rest and after pacing. Pacing drastically reduced wall motion in well collateralized LAD occlusions if sets of paired observations are compared ( $p < 0.05$  respectively  $< 0.01$ ). Poorly collateralized occlusions however showed severely depressed wall motion at rest and remained unchanged after stress ( $p > 0.05$ ).

Table IV summarizes clinical data of two patient groups with comparable numbers and localizations of coronary occlusions separated by the presence or absence of good collaterals. Patients with good collaterals to the occluded vessels have more severe angina ( $p < 0.001$ ) and more severe ST segment changes during exercise ( $p < 0.01$ ) than patients with poor collaterals. Patients with poor collaterals have more severe dyspnea ( $p < 0.01$ ) and more histories of previous infarctions if compared to patients with good collaterals ( $p < 0.001$ ).

## Discussion

A well-developed collateral circulation supplying the distal segment of a completely

**Table I** Ejection fraction at rest in patients with coronary artery occlusions and different stages of collateralization

| Occluded vessel          | Good collaterals |                       | Poor collaterals |                   | P values    |
|--------------------------|------------------|-----------------------|------------------|-------------------|-------------|
|                          | Pat. No.         | Ejection fraction (%) | Pat. No.         | Ejection fraction |             |
| LAD                      | 9                | $59.6 \pm 2.3$        | 22               | $41.4 \pm 1.4$    | $p < 0.001$ |
| LC                       | 4                | $66.5 \pm 3.7$        | 4                | $41.0 \pm 4.0$    | —           |
| RC                       | 11               | $67.8 \pm 2.1$        | 10               | $51.0 \pm 2.6$    | $p < 0.001$ |
| LAD + RC                 | 4                | $69.0 \pm 3.3$        | 4                | $29.0 \pm 1.4$    | —           |
| LAD + LC                 | 3                | $47.7 \pm 2.1$        | 6                | $34.7 \pm 3.4$    | —           |
| RC + LC                  | 3                | $57.7 \pm 3.7$        | 5                | $45.0 \pm 2.6$    | —           |
| LAD + RC + LC            | 1                | 47.0                  | 1                | 33.0              | —           |
| Normal coronary arteries | 17               | $65.2 \pm 1.9$        |                  |                   |             |

Abbreviations: LAD = anterior descending branch of the left coronary artery; LC = circumflex branch of the left coronary artery; RC = right coronary artery; Pat. No. = number of patients.

—  $p < 0.001$  or  $p > 0.05$  denotes significant differences if compared to the ejection fraction of patients with normal coronary arteries.

Mean values  $\pm$  S.E.M.

occluded coronary artery preserves myocardial function partially. Preservation of myocardial function at rest was demonstrated by a normal ejection fraction, a nearly normal regional wall motion and a low incidence of past myocardial infarctions. During stress the limited capacity of good collaterals was detected by a drastic fall of segmental wall motion after pacing and severe ST segment changes during treadmill exercise.

From dog experiments it is known that during gradual occlusion of a major coronary artery collaterals enlarge rather rapidly by an active growth process.<sup>3</sup> The degree to which collaterals can protect the myocardium depends on the time available for their development.<sup>12,13</sup> The higher the speed of the occlusion, the lower the chance for collaterals to compensate for it.<sup>14</sup> Quantification of the protective effect of collaterals on myocardial function during life requires comparison of patients with equal degree of coronary artery disease but with and without collaterals. Since the severity of coronary stenoses is difficult to measure angiographically we investigated only patients with complete coronary artery occlusions. In addition we believe that the effect of coronary collateral circulation can be evaluated in complete coronary artery occlusion



Fig 2 Well collateralized occlusion of the circumflex branch of the left coronary artery. The occluded circumflex branch (arrow) shows complete retrograde filling from diagonal branches (arrowhead). In this case not a single large collateral vessel was found but an extensive collateral network was discovered instead. In addition atrial collaterals to the right coronary artery are opacified.

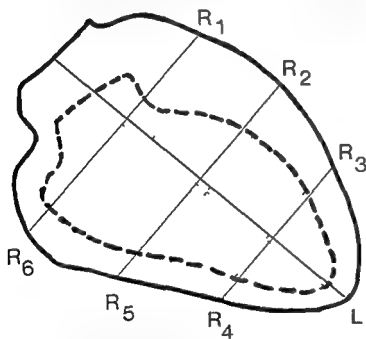


Fig 3 End diastolic and end systolic silhouettes are depicted with the system of hemiaxes.

were drawn for each silhouette (Fig 3). The percentage shortening was calculated as diastolic minus systolic axis divided by diastolic axis times 100 per cent.

Clinical data of patients with comparable numbers and localizations of coronary artery occlusions but different stages of collateralization

were reviewed from 87 investigated patients to get two groups with comparable severity of coronary artery disease: twenty patients had good and 27 had poor collaterals. The history of angina pectoris and dyspnea was graded according to the NYHA. Any history of previous myocardial infarction was noted based on clinical, electrographic and enzymatic data. A treadmill exercise test was performed according to Kasser and Bruce<sup>10</sup> with continuous ECG monitoring. The ST segment changes after submaximal exercise were measured and averaged over at least 10 beats.

### Results

Well collateralized occlusions were found in 35 patients; poorly or not collateralized occlusions were found in 52 patients.

Table I presents the average values of biplane ejection fraction at rest and the distribution into seven subgroups with various combinations of complete coronary occlusions separated by the degree of collateralization. Well collateralized LAD occlusions were found less frequently (nine patients) than poorly collateralized LAD occlusions (22 patients). Well collateralized RC occlusions (11 patients) were found with equal frequency compared to poorly collateralized RC

between our results and those of Helfant and colleagues<sup>2</sup> Lavine and co workers<sup>3</sup> and Carroll and associates<sup>4</sup>. These studies investigated patients with stenoses greater than 75 per cent Helfant and colleagues and Lavine and co workers<sup>3</sup> subdivided collaterals into present or absent Carroll and associates differentiated four collateral classes (no poor fair good) The groups with collaterals showed an equal or increased number of abnormal ventriculograms as compared to the group without collaterals The conclusion was that collaterals do not protect from the development of ventricular asynergy This disagreement is probably due to the different patient populations studied (stenoses of more than 75 per cent or complete occlusion in our study) and to the different gradations used for collaterals

Our clinical data revealed a high incidence of severe angina and marked ST segment changes during exercise in patients with good collateralization In addition pacing stress induced a marked reduction of wall motion indicative of acute myocardial ischemia in the patients These findings are in accordance with the experience of others who reported no protective effect of coronary collaterals against acute myocardial ischemia as measured by treadmill stress test This implies that the area perfused by good collaterals mainly consisting of viable myocardium becomes ischemic since collaterals are not able to increase their flow capacity proportional to the increased oxygen demands

### Summary

The influence of coronary collateral vessels on resting left ventricular function was investigated in 87 consecutive patients with complete coronary artery occlusion of at least one of the three major coronary vessels The morphology of coronary and collateral circulation was evaluated by coronary arteriography Left ventricular function was assessed by biplane ejection fraction and segmental wall motion was evaluated by hemi axes shortening Collaterals to occluded arteries were graded as good or poor according to the caliber of the distal vessel segment Patients were divided into those with good collaterals ( $n = 35$ ) and those with poor or absent collaterals ( $n = 52$ ) furthermore these two groups were subdivided according to the location of coronary artery occlusion Collateralized single vessel

Table IV Clinical data of patients with equal numbers and localizations of coronary artery occlusions and different stages of collateralization

|                                  | Good collaterals | Poor collaterals | P values |
|----------------------------------|------------------|------------------|----------|
| Anginal pain (NYHA Class)        | 34 ± 0.4†        | 13 ± 0.3         | <0.001   |
| Exercise test (ST changes in mV) | 0.30 ± 0.04      | 0.13 ± 0.03      | <0.01    |
| Dyspnea (NYHA Class)             | 0.6 ± 0.1        | 1.9 ± 0.3        | <0.01    |
| History of previous infarction   | 20%              | 89%              | <0.001   |

†Mean values ± SEM

occlusions were found more frequently than collateralized multiple vessel occlusions Ejection fraction and segmental wall motion was significantly better in well collateralized occlusions than in poorly collateralized occlusions of LAD or RC and was normal or depressed only slightly if compared to 17 patients without heart disease In contrast total and regional myocardial function was severely depressed in poorly collateralized LAD or RC occlusion Ventriculography after rapid ventricular pacing was performed in 12 of 87 patients with well collateralized or poorly collateralized LAD occlusion to evaluate to what extent coronary collaterals protect anterior wall motion during increased oxygen demand Pacing induced a drastic fall of anterior wall motion in well collateralized segments whereas no change was found in poorly collateralized segments Reviewing clinical data of two patient groups with comparable numbers and locations of occlusions revealed in the well collateralized group more severe angina ( $p < 0.001$ ) and ST segment changes during exercise ( $p < 0.01$ ) than in the poorly collateralized group The latter showed more severe dyspnea ( $p < 0.01$ ) and more histories of previous infarctions ( $p < 0.001$ ) We conclude that well developed collateral vessels to a complete occluded artery prevent severe asynergy at rest but not during stress

### REFERENCES

- McGregor M The coronary collateral circulation A significant compensatory mechanism or a functionless quirk of nature *Circulation* 52:579 1975
- Helfant R H Kemp H G and Gorlin R Coronary atherosclerosis coronary collaterals and their relation to cardiac function *Ann Intern Med* 73:189 1970
- Helfant R H Yokoyama P S and Gorlin R Func

**Table II** Segmental wall motion at rest in patients with coronary artery occlusion and different stages of collateralization

|                          |                  | Shortening of hemiaxes |                |                |               |                |              |            |
|--------------------------|------------------|------------------------|----------------|----------------|---------------|----------------|--------------|------------|
|                          |                  | R <sub>1</sub>         | R <sub>2</sub> | R <sub>3</sub> | R             | R <sub>s</sub> | R            | L          |
| LAD Occlusion            | Good collaterals | 47.4 ± 3.8†            | 33.0 ± 2.3     | 36.1 ± 2.3     | 46.3 ± 5.9    | 39.8 ± 3.7     | 20.8 ± 4.0   | 12.7 ± 1.9 |
|                          | Poor collaterals | 26.4 ± 4.3 *           | 11.9 ± 3.1 *   | 9.8 ± 3.3***   | 28.5 ± 5.8    | 36.4 ± 2.9     | 26.8 ± 1.7   | 8.3 ± 1.0  |
| P values                 |                  | <0.01                  | <0.001         | <0.001         | ns            | ns             | ns           | <0.05      |
| RC Occlusion             | Good collaterals | 55.7 ± 4.1             | 47.0 ± 4.8     | 45.7 ± 3.9     | 35.9 ± 3.6    | 30.3 ± 3.6     | 21.9 ± 2.8   | 20.6 ± 1.3 |
|                          | Poor collaterals | 43.9 ± 5.9             | 36.2 ± 5.4     | 40.1 ± 5.3     | 10.7 ± 4.8*** | 5.9 ± 3.0*     | 13.1 ± 2.9 * | 16.4 ± 1.6 |
| P values                 |                  | ns                     | ns             | ns             | <0.001        | <0.001         | <0.05        | ns         |
| Normal coronary arteries |                  | 52.6 ± 5.7             | 47.0 ± 4.1     | 42.1 ± 2.5     | 34.0 ± 3.2    | 32.3 ± 3.1     | 27.0 ± 2.8   | 19.4 ± 3.4 |

Abbreviations: LAD = anterior descending branch of the left coronary artery; RC = right coronary artery

\*p &lt; 0.05; †p &lt; 0.01; \*\*\*p &lt; 0.001 denotes significant differences between the groups with occluded vessels and patients with normal coronary arteries

†Mean values ± SEM

**Table III** Anterior wall motion at rest and after pacing in patients with LAD occlusion and different stages of collateralization

|          | Shortening of hemiaxes (%) |            |                |           |                  |            |           |           |
|----------|----------------------------|------------|----------------|-----------|------------------|------------|-----------|-----------|
|          | Good collaterals           |            |                |           | Poor collaterals |            |           |           |
|          | R                          | R          | R <sub>s</sub> | L         | R                | R          | R         | L         |
| Rest     | 56.2 ± 3.9†                | 36.0 ± 2.5 | 32.0 ± 4.1     | 9.8 ± 2.6 | 26.7 ± 9.1       | 10.0 ± 4.0 | 4.0 ± 2.7 | 6.2 ± 0.7 |
| Pacing   | 25.8 ± 6.5                 | 15.7 ± 3.5 | 10.3 ± 6.1     | 5.8 ± 1.1 | 20.2 ± 5.0       | 9.5 ± 3.6  | 3.0 ± 2.4 | 5.8 ± 1.4 |
| P values | <0.01                      | <0.01      | <0.05          | ns        | ns               | ns         | ns        | ns        |

†Mean values ± SEM

only, since any additional flow through coronary stenoses may contribute to preservation of myocardial function. In the dog heart it could be demonstrated that maximal collateral flow to the perfusion beyond a stenosis is not achieved before the vessel is completely occluded.<sup>20</sup>

Patients with well collateralized occlusions showed higher ejection fractions, better regional wall motion and a smaller percentage of previous myocardial infarctions in contrast to patients with poor collaterals. The latter patients had severely depressed myocardial function. Their dysfunction is caused by severe loss of wall motion in the area previously supplied by the occluded artery. The loss of wall motion associated with a high incidence of previous infarctions suggests that synergism in these patients is a result of myocardial fibrosis. This is confirmed by

results of Starr and associates<sup>21</sup> who found in 35 of 36 patients with severe left ventricular segmental contraction abnormalities significant myocardial fibrosis in the corresponding left ventricular wall at autopsy.

Our results are in agreement with the findings of others. Levin<sup>10</sup> reported normal contractility at rest in 43 per cent, hypokinesia in 52 per cent and akinesia in 5 per cent of 86 completely occluded adequately collateralized arteries while occlusions with inadequate collaterals showed normal contractility in only 11 per cent, hypokinesia in 16 per cent and akinesia in 73 per cent. Gensini and da Costa<sup>8</sup> described five patients with completely obstructed arteries and collaterals with normal resting electrocardiograms while all patients without collaterals had abnormal electrocardiograms. There is considerable disagreement

between our results and those of Helfant and colleagues 'Lavine and co workers' and Carroll and associates<sup>4</sup>. These studies investigated patients with stenoses greater than 75 per cent. Helfant and colleagues and Lavine and co workers subdivided collaterals into present or absent. Carroll and associates<sup>4</sup> differentiated four collateral classes (no poor fair good). The groups with collaterals showed an equal or increased number of abnormal ventriculograms as compared to the group without collaterals. The conclusion was that collaterals do not protect from the development of ventricular asynergy. This disagreement is probably due to the different patient populations studied (stenoses of more than 75 per cent or complete occlusion in our study) and to the different gradations used for collaterals.

Our clinical data revealed a high incidence of severe angina and marked ST segment changes during exercise in patients with good collateralization. In addition pacing stress induced a marked reduction of wall motion indicative of acute myocardial ischemia in these patients. These findings are in accordance with the experience of others who reported no protective effect of coronary collaterals against acute myocardial ischemia as measured by treadmill stress test. This implies that the area perfused by good collaterals mainly consisting of viable myocardium becomes ischemic since collaterals are not able to increase their flow capacity proportional to the increased oxygen demands.

### Summary

The influence of coronary collateral vessels on resting left ventricular function was investigated in 87 consecutive patients with complete coronary artery occlusion of at least one of the three major coronary vessels. The morphology of coronary and collateral circulation was evaluated by coronary arteriography. Left ventricular function was assessed by biplane ejection fraction and segmental wall motion was evaluated by hemi-axes shortening. Collaterals to occluded arteries were graded as good or poor according to the caliber of the distal vessel segment. Patients were divided into those with good collaterals ( $n = 35$ ) and those with poor or absent collaterals ( $n = 52$ ); furthermore these two groups were subdivided according to the location of coronary artery occlusion: Collateralized single vessel

**Table IV** Clinical data of patients with equal numbers and localizations of coronary artery occlusions and different stages of collateralization

|                                  | Good collaterals | Poor collaterals | P values |
|----------------------------------|------------------|------------------|----------|
| Anginal pain (NYHA Class)        | 34 $\pm$ 0.21    | 13 $\pm$ 0.3     | <0.001   |
| Exercise test (ST changes in mV) | 0.30 $\pm$ 0.04  | 0.13 $\pm$ 0.03  | <0.01    |
| Dyspnea (NYHA Class)             | 0.6 $\pm$ 0.2    | 1.9 $\pm$ 0.3    | <0.01    |
| History of previous infarction   | 90%              | 80%              | <0.001   |

† Mean  $\pm$  SEM

occlusions were found more frequently than collateralized multiple vessel occlusions. Ejection fraction and segmental wall motion was significantly better in well collateralized occlusions than in poorly collateralized occlusions of LAD or RC and was normal or depressed only slightly if compared to 17 patients without heart disease. In contrast total and regional myocardial function was severely depressed in poorly collateralized LAD or RC occlusion. Ventriculography after rapid ventricular pacing was performed in 12 of 87 patients with well collateralized or poorly collateralized LAD occlusion to evaluate to what extent coronary collaterals protect anterior wall motion during increased oxygen demand. Pacing induced a drastic fall of anterior wall motion in well collateralized segments whereas no change was found in poorly collateralized segments. Reviewing clinical data of two patient groups with comparable numbers and locations of occlusions revealed in the well collateralized group more severe angina ( $p < 0.001$ ) and ST segment changes during exercise ( $p < 0.01$ ) than in the poorly collateralized group. The latter showed more severe dyspnea ( $p < 0.01$ ) and more histories of previous infarctions ( $p < 0.001$ ). We conclude that well developed collateral vessels to a complete occluded artery prevent severe asynergy at rest but not during stress.

### REFERENCES

- McGregor M. The coronary collateral circulation: A significant compensatory mechanism or a functionless quirk of nature. *Circulation* 52:579, 1975.
- Helfant, R. H., Kemp H. G. and Gorlin R. Coronary atherosclerosis: coronary collaterals and their relation to cardiac function. *Ann Intern Med* 73:189, 1970.
- Helfant, R. H., Yokonas P. S. and Gorlin R. Func-



Table II Segmental wall motion at rest in patients with coronary artery occlusion and different stages of collateralization

|                          |                  | Shortening of hemiaxes |                |           |                |            |          |          |
|--------------------------|------------------|------------------------|----------------|-----------|----------------|------------|----------|----------|
|                          |                  | R                      | R <sub>1</sub> | R         | R <sub>1</sub> | R          | R        | L        |
| LAD Occlusion            | Good collaterals | 474 ± 38†              | 330 ± 23       | 361 ± 23  | 463 ± 59       | 398 ± 37   | 208 ± 40 | 127 ± 19 |
|                          | Poor collaterals | 264 ± 43               | 119 ± 31 *     | 98 ± 33 * | 285 ± 56       | 364 ± 29   | 268 ± 17 | 83 ± 10  |
| P values                 |                  | <0.01                  | <0.001         | <0.001    | ns             | ns         | ns       | <0.05    |
| RC Occlusion             | Good collaterals | 517 ± 41               | 470 ± 48       | 457 ± 39  | 359 ± 36       | 303 ± 36   | 219 ± 28 | 206 ± 13 |
|                          | Poor collaterals | 439 ± 59               | 362 ± 54       | 401 ± 53  | 107 ± 48       | 59 ± 30 ** | 131 ± 29 | 164 ± 16 |
| P values                 |                  | ns                     | ns             | ns        | <0.001         | <0.001     | <0.05    | ns       |
| Normal coronary arteries |                  | 526 ± 57               | 470 ± 41       | 421 ± 25  | 340 ± 32       | 323 ± 31   | 270 ± 28 | 194 ± 34 |

Abbreviations LAD = anterior descending branch of the left coronary artery RC = right coronary artery  
 \*  $p < 0.05$  \*\*  $p < 0.01$  \*\*\*  $p < 0.001$  denotes significant differences between the groups with occluded vessels and patients with normal coronary arteries

†Mean values ± SEM

Table III Anterior wall motion at rest and after pacing in patients with LAD occlusion and different stages of collateralization

|          | Shortening of hemiaxes (%) |                |                |           |                  |            |           |           |
|----------|----------------------------|----------------|----------------|-----------|------------------|------------|-----------|-----------|
|          | Good collaterals           |                |                |           | Poor collaterals |            |           |           |
|          | R                          | R <sub>1</sub> | R <sub>2</sub> | L         | R                | R          | R         | L         |
| Rest     | 56.2 ± 3.9†                | 36.0 ± 2.5     | 32.0 ± 4.1     | 9.8 ± 2.6 | 26.7 ± 9.1       | 10.0 ± 4.0 | 4.0 ± 2.7 | 6.2 ± 0.7 |
| Pacing   | 21.8 ± 6.5                 | 15.7 ± 3.5     | 10.3 ± 6.1     | 5.8 ± 1.1 | 20.2 ± 5.0       | 9.5 ± 3.6  | 3.0 ± 2.4 | 5.8 ± 1.4 |
| P values | <0.01                      | <0.01          | <0.05          | ns        | ns               | ns         | ns        | ns        |

†Mean values ± SEM

only since any additional flow through coronary stenoses may contribute to preservation of myocardial function. In the dog heart it could be demonstrated that maximal collateral flow to the perfusion beyond a stenosis is not achieved before the vessel is completely occluded.<sup>20</sup>

Patients with well collateralized occlusions showed higher ejection fractions, better regional wall motion and a smaller percentage of previous myocardial infarctions in contrast to patients with poor collaterals. The latter patients had severely depressed myocardial function. Their dysfunction is caused by severe loss of wall motion in the area previously supplied by the occluded artery. The loss of wall motion associated with a high incidence of previous infarctions suggests that asynergy in these patients is a result of myocardial fibrosis. This is confirmed by

results of Starr and associates<sup>11</sup> who found in 35 of 36 patients with severe left ventricular segmental contraction abnormalities significant myocardial fibrosis in the corresponding left ventricular wall at autopsy.

Our results are in agreement with the findings of others. Levin<sup>10</sup> reported normal contractility at rest in 43 per cent, hypokinesia in 52 per cent and akinesia in 5 per cent of 86 completely occluded adequately collateralized arteries while occlusions with inadequate collaterals showed normal contractility in only 11 per cent, hypokinesia in 16 per cent and akinesia in 73 per cent. Ginsini and da Costa<sup>2</sup> described five patients with completely obstructed arteries and collaterals with normal resting electrocardiograms while all patients without collaterals had abnormal electrocardiograms. There is considerable disagreement

between our results and those of Helfant and colleagues Lavine and co workers and Carroll and associates. These studies investigated patients with stenoses greater than 75 per cent Helfant and colleagues and Lavine and co workers subdivided collaterals into present or absent Carroll and associates differentiated four collateral classes (no poor fair good). The groups with collaterals showed an equal or increased number of abnormal ventriculograms as compared to the group without collaterals. The conclusion was that collaterals do not protect from the development of ventricular asynergy. This disagreement is probably due to the different patient populations studied (stenoses of more than 70 per cent or complete occlusion in our study) and to the different gradations used for collaterals.

Our clinical data revealed a high incidence of severe angina and marked ST segment changes during exercise in patients with good collateralization. In addition pacing stress induced a marked reduction of wall motion indicative of acute myocardial ischemia in these patients. These findings are in accordance with the experience of others who reported no protective effect of coronary collaterals against acute myocardial ischemia as measured by treadmill stress test. This implies that the area perfused by good collaterals mainly consisting of viable myocardium becomes ischemic since collaterals are not able to increase their flow capacity proportional to the increased oxygen demands.

### Summary

The influence of coronary collateral vessels on resting left ventricular function was investigated in 87 consecutive patients with complete coronary artery occlusion of at least one of the three major coronary vessels. The morphology of coronary and collateral circulation was evaluated by coronary arteriography. Left ventricular function was assessed by biplane ejection fraction and segmental wall motion was evaluated by hemiaxes shortening. Collaterals to occluded arteries were graded as good or poor according to the caliber of the distal vessel segment. Patients were divided into those with good collaterals ( $n = 35$ ) and those with poor or absent collaterals ( $n = 52$ ). Furthermore these two groups were subdivided according to the location of coronary artery occlusion. Collateralized single vessel

**Table IV** Clinical data of patients with equal numbers and localizations of coronary artery occlusions and different stages of collateralization

|                                  | Good collaterals       | Poor collaterals | P values |
|----------------------------------|------------------------|------------------|----------|
| Anginal pain (NYHA Class)        | $34 \pm 0.7^{\dagger}$ | $13 \pm 0.3$     | $<0.001$ |
| Exercise test (ST changes in mV) | $0.30 \pm 0.04$        | $0.13 \pm 0.03$  | $<0.01$  |
| Dyspnea (NYHA Class)             | $0.6 \pm 0.2$          | $1.9 \pm 0.3$    | $<0.01$  |
| History of previous infarction   | 70%                    | 89%              | $<0.001$ |

$^{\dagger}$ Mean values  $\pm$  SEM

occlusions were found more frequently than collateralized multiple vessel occlusions. Ejection fraction and segmental wall motion was significantly better in well collateralized occlusions than in poorly collateralized occlusions of LAD or RC and was normal or depressed only slightly if compared to 17 patients without heart disease. In contrast total and regional myocardial function was severely depressed in poorly collateralized LAD or RC occlusion. Ventriculography after rapid ventricular pacing was performed in 12 of 87 patients with well collateralized or poorly collateralized LAD occlusion to evaluate to what extent coronary collaterals protect anterior wall motion during increased oxygen demand. Pacing induced a drastic fall of anterior wall motion in well collateralized segments whereas no change was found in poorly collateralized segments. Reviewing clinical data of two patient groups with comparable numbers and locations of occlusions revealed in the well collateralized group more severe angina ( $p < 0.001$ ) and ST segment changes during exercise ( $p < 0.01$ ) than in the poorly collateralized group. The latter showed more severe dyspnea ( $p < 0.01$ ) and more histories of previous infarctions ( $p < 0.001$ ). We conclude that well developed collateral vessels to a complete occluded artery prevent severe asynergy at rest but not during stress.

### REFERENCES

- McGregor M. The coronary collateral circulation. A significant compensatory mechanism or a functionless quirk of nature. *Circulation* 52:593-195.
- Helfant R. H., Kemp H. G. and Gorlin R. Coronary atherosclerosis, coronary collaterals and their relation to cardiac function. *Ann Intern Med* 73:189-190.
- Helfant R. H., Tokotas P. S. and Gorlin R. Func

- tional importance of the human coronary collateral circulation *N Engl J Med* 284 1277 1971
- 4 Harris CN Kaplan M A Parker D P Aronow W S and Elletstad M H Anatomic and functional correlates of intercoronary collateral vessels *Am J Cardiol* 30 611 1972
  - 5 Lavine P Filip Z Najmi M Kimbiris D Segal B L and Linhart J W Clinical and hemodynamic evaluation of coronary collateral vessels in coronary artery disease *Am Heart J* 87 343 1974
  - 6 Carroll R J Verani M S and Palestini H L The effect of collateral circulation on segmental left ventricular contraction *Circulation* 50 709 1974
  - 7 Vismara L A Miller R R De Maria A N Forrester J M Amsterdam E A and Mason D T Collateral circulation in chronic coronary disease effects on segmental left ventricular contractile function *Am J Cardiol* 35 174 1975
  - 8 Gensini G G and da Costa B C B The coronary collateral circulation in living man *Am J Cardiol* 24 393 1969
  - 9 Levin D C Sos T A Lee J G and Baltaxe H A Coronary collateral circulation and distal coronary runoff the key factors in preserving myocardial contractility in patients with coronary artery disease *Am J Roentgenol Radium Ther Nucl Med* 119 474 1973
  - 10 Levin D C Pathways and functional significance of the coronary collateral circulation *Circulation* 50 831 1974
  - 11 Gander M P Ham E and Judkins M P Coronary pathology in patients with coronary heart disease (Abstr) *Am J Cardiol* 33 138 1974
  - 12 Gregg D E Thornton J J and Mautz F R The magnitude adequacy and source of the collateral blood flow and pressure in chronically occluded coronary arteries *Am J Physiol* 127 161 1930
  - 13 Elliot E C Jones E L Bloor C M Leon A S and Gregg D E Day to day changes in coronary hemodynamics secondary to constriction of circumflex branch of left coronary artery in conscious dogs *Circ Res* 22 237 1968
  - 14 Schaper W The collateral circulation of the heart New York Amsterdam 1971 American Elsevier Company
  - 15 Becker L C and Pitt II Collateral blood flow in conscious dogs with chronic coronary artery occlusion *Am J Physiol* 221 1507 1971
  - 16 Khouri E M Gregg D E and Mcgranahan Jr G M Regression and reappearance of coronary collaterals *Am J Physiol* 220 655 1971
  - 17 Schaper W Lewis P Flameng W and Guyton L Myocardial steal produced by coronary vasodilation in chronic coronary artery occlusion *Basic Res Cardiol* 68 3 1973
  - 18 Flameng W Schaper W and Lewis P Multiple experimental coronary occlusion without infarction *Am Heart J* 85 767 1973
  - 19 Flameng W and Wusten B Postischemic reactive hyperemia in dogs with multiple chronic coronary artery occlusion without infarction *Circulation* 49 and 50 III 173 1974
  - 20 Elliot E C Khouri E M Snow J A and Gregg D E Direct measurement of coronary collateral blood flow in conscious dogs by an electromagnetic flowmeter *Circ Res* 34 374 1974
  - 21 Myers R W, Scherer J L Goldstein R A Goldstein R E Kent K M and Epstein N Effects of nitroglycerin and nitroglycerin-methoxamine during acute myocardial ischemia in dogs with preexisting multivessel coronary occlusive disease *Circulation* 51 632 1975
  - 22 Flameng W Wusten B Winkler B Paszyk S and Schaper W Influence of perfusion pressure and heart rate on local myocardial flow in the collateralized heart with chronic coronary occlusion *Am Heart J* 89 51 1975
  - 23 Schwarz F Flameng W Mack B Turschmann W and Schaper W Vascular and cardiac contractile reserve in the dog heart with multiple coronary occlusion *Am Heart J* 92 600 1976
  - 24 Schlesinger M J An injection plus dissection study of coronary artery occlusions and anastomoses *Am Heart J* 15 528 1938
  - 25 Blumgart H L Schlesinger M J and Davis D Studies on the relation of the clinical manifestations of angina pectoris coronary thrombosis and myocardial infarction to the pathologic findings *Am Heart J* 19 1 1940
  - 26 Zoll P M Wessler S and Schlesinger M J Interarterial coronary anastomoses in the human heart with particular reference to anemia and relative cardiac anoxia *Circulation* 4 797 1951
  - 27 Brodski G Mantero O and Scomazzoni G The collaterals of the coronary arteries in normal and pathologic hearts *Circ Res* 4 223 1956
  - 28 Fulton W F M The coronary arteries Springfield Ill 1965 Charles C Thomas Publisher
  - 29 Schwarz F Enslin R and Thormann J Der Einfluss des Kollateralkreislaufes auf die totale und regionale Myokardfunktion bei koronarer Herzkrankheit *Schweiz Med Wochenschr* 106 1407 1976
  - 30 Goldstein R E Stinson E H Scherer J L Senigen R P Gohl T M and Epstein S E Intraoperative coronary collateral function in patients with coronary occlusive disease Nitroglycerin responsiveness and angiographic correlations *Circulation* 49 298 1974
  - 31 Gensini G C Esente P Delmonico E Jr Parker F B Neville J F Eich R H and Webb W R Coronary collaterals and coronary backflow recordings in patients with coronary artery disease A double blind angiographic surgical correlation (Abstr) *Am J Cardiol* 31 134 1973
  - 32 Cannon P J Suaccia R R Fowler D L Wers M H Schmidt D H and Casarella W J Measurement of regional myocardial blood flow in man description and critique of the method using venous 133 and a scintillation camera *Am J Cardiol* 36 783 1975
  - 33 Cannon P J Dell R H and Dwyer E M Jr Regional myocardial perfusion rates in patients with coronary artery disease *J Clin Invest* 51 978 1972
  - 34 Schmidt D H Weiss M H Casarella W J Fowler D L Suaccia R R and Cannon P J Regional myocardial perfusion during atrial pacing in patients with coronary artery disease *Circulation* 53 807 1976
  - 35 Judkins M P Percutaneous transluminal selective coronary arteriography *Radiolog Clin North Am* 6 467 1968
  - 36 Cohn P I Gorlin R Adams D F Chahine R A Vokonas P E and Herman M V Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease *Am J Cardiol* 33 1 1974
  - 37 Sandler H and Dodge H T The use of single plane angiocardigrams for the calculation of left ventricular volume in man *Am Heart J* 75 322 1968
  - 38 Herrman M V and Gorlin R Implication of left ventricular synergy *Am J Cardiol* 23 38 1969

- 39 Hasser I S and Bruce R A The comparative effects of aging and coronary heart disease on submaximal and maximal exercise Circulation 39 759 1969
- 40 See J R Marlon A M Feikes H L and Cosby R S Effect of direct revascularization surgery on coronary collateral circulation in man Am J Cardiol 36 734 1975
- 41 Starr J V Wagner G S and Hackel D B Pathologic significance of arteriographic coronary artery lesions and segmental ventricular contraction abnormalities (Abstr) Circulation 49 and 50 111 150 1974
- 42 Berne R M and Rubio R Acute coronary occlusion early changes that induce coronary dilatation and the development of collateral circulation Am J Cardiol 24 76 1969
- 43 Schaper W De Brahandt M and Lewi P DNA synthesis and mitoses in coronary collateral vessels of the dog Circ Res 28 611 1971
- 44 Bourassa M G Solovuev A Goulet C and Leperance J Regression and appearance of coronary collateral in humans during life Circulation 49 and 50 (Suppl) 11 197 1974
- 45 Gensini C G Cited in ref 44 Discussion Circulation 49 and 50 (Suppl) 11 134 1974

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center Inc, P O Box 767, Schenectady, NY 12301, 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works, or for resale.

# Echocardiography in chronic alcoholics following prolonged periods of abstinence

William C Reeves MD  
Navin C Nanda MD  
Raymond Gramiak, MD  
Rochester N Y

Left ventricular studies utilizing M mode echocardiography have proved valuable in the noninvasive assessment of left ventricular function.<sup>1-5</sup> Furthermore recent investigation supports echocardiography as a sensitive technique for detecting small changes in left ventricular end diastolic volumes.<sup>6</sup> Systolic time intervals derived conventionally from simultaneous recordings of the carotid pulse and the ECG have also been useful in the evaluation of left ventricular function.<sup>7-9</sup> These intervals can also be conveniently and accurately derived from echocardiographic recordings of the aortic root.<sup>10-12</sup> McDonald and Hobson<sup>13</sup> have concluded that the combined information derived from the measurement of left ventricular dimensions and systolic time intervals was superior to either method used alone.

Alcohol has been incriminated as an etiologic factor in the development of left ventricular failure by a direct cardiotoxic effect.<sup>14-18</sup> Abnormalities of left ventricular function have been documented utilizing both invasive and noninvasive methods in chronic alcoholics.<sup>19-21</sup> Transient depression of left ventricular function has also been noted in normal volunteers immediately following alcohol consumption.<sup>22</sup>

From the Cardiology Unit, Department of Medicine and the Department of Radiology, University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester, N Y.

This work was supported by contract HL 05500 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Md.

Received for publication Mar 15 1977

Accepted for publication Apr 11 1977

Reprint requests: Dr Navin C Nanda, Cardiology Unit, Box 69, Strong Memorial Hospital, 601 Elmwood Avenue, Rochester, N Y 14642.

Although alcohol is known to freely pass the placental barrier,<sup>23</sup> no analysis of left ventricular function has been made in children born of alcoholic mothers.

We have elected to utilize echocardiographic techniques of left ventricular function in studying chronic asymptomatic alcoholics following a long period of abstinence and a small group of asymptomatic children born of chronic alcoholic mothers who were actively drinking during their pregnancy.

## Materials and methods

Twenty six adult volunteers (19 men and 7 women, mean age 45 years, range 25 to 62 years) form the basis of this study. The duration of active alcoholism in these individuals averaged 18.3 years (range 4 to 40 years). Their mean duration of abstinence from alcohol was 3.1 years (range 3 months to 17 years) (Table I). Additionally seven asymptomatic children born of four alcoholic mothers belonging to the above group who were drinking throughout their pregnancy was also included in the study. Their average age was 14.1 years (range 4 to 19 years). A comparison group of age matched normal individuals (13 adults and 8 children) was also studied.

A detailed medical history, physical examination, 12 lead ECG and an echocardiographic examination performed in the standard manner were obtained in all.

All echo examinations were performed with a commercially available Picker echograph and a 2.25 m Hz transducer. Continuous records were obtained at 125 mm/sec on 35 mm film using a slave oscilloscope and a Fairchild record camera.

The following echo parameters were studied (Figs 1 and 2)

1 Percentage of left ventricular dimension shortening (per cent  $\Delta S$ )<sup>2</sup>

$$\% \Delta S = \frac{D_s - D_d}{D_d} \times 100$$

The left ventricular diastolic dimension ( $D_d$ ) measured in mm was the perpendicular distance between the left septal and left ventricular posterior wall endocardial surfaces measured at the R wave peak of a simultaneously recorded ECG. The left ventricular systolic dimension ( $D_s$ ) was measured in mm as the shortest perpendicular distance between the endocardial surfaces of the left side of the ventricular septum and the left ventricular posterior wall during systole.

2 Left ventricular ejection fraction (EF)

$$EF = \frac{D_s - D_d}{D_d} \times 100$$

3 Mean velocity of circumferential fiber shortening (mean  $V_{cf}$ )

$$\text{mean } V_{cf} = \frac{D_s - D_d}{D_d \times dt}$$

This was expressed in circumferences/second. Left ventricular ejection time (dt) measured in msec was the period from the onset of systolic anterior motion of the left ventricular posterior wall to its maximal anterior excursion.

4 Systolic velocities of the ventricular septum and left ventricular posterior wall. These were measured in mm/sec as the maximal slope of the endocardial surfaces of the ventricular septum and left ventricular posterior wall respectively during systole.

5 Excursion of the ventricular septum and left ventricular posterior wall. These were measured in mm as the maximum perpendicular distance from the diastolic endocardial surface of the ventricular septum and left ventricular posterior wall to the level of their maximal systolic excursions.

6 The systolic time interval ratio (PEP/LVET). Pre-ejection period (PEP) measured in msec was the interval from the onset of the Q wave of the ECG to the point of opening of the aortic valve on the echogram. Left ventricular ejection time (LVET) measured in msec was the interval from the opening to the closing of the aortic valve on the echogram.

7 Ventricular septal thickness<sup>3</sup>. This was measured in mm as the distance between the right and left endocardial surfaces of the ventric

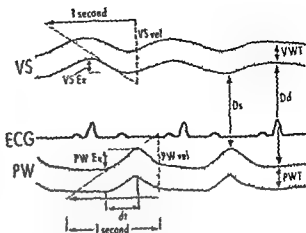


Fig 1 Diagram showing relationship between ECG tracing and echocardiographic measurements. VS = ventricular septum VS Ex = maximal excursion of ventricular septum VS vel = maximal systolic velocity of the ventricular septum PW = left ventricular posterior wall PW Ex = maximal excursion of the left ventricular posterior wall PW vel = maximal systolic velocity of the left ventricular posterior wall PWT = posterior wall thickness VIT = ventricular septal thickness Dd = end-diastolic dimension Ds = end-systolic dimension dt = duration of left ventricular systole

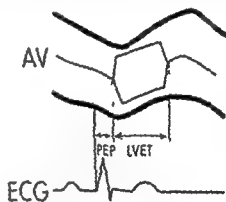


Fig 2 Diagram showing relationship between ECG tracing and echocardiographic measurements. AV = aortic valve PEP = pre-ejection period LVET = left ventricular ejection time

ular septum at the time of the R wave peak from a simultaneously recorded ECG.

8 Left ventricular posterior wall thickness<sup>3</sup>. This was measured in mm as the distance from left ventricular endocardial to epicardial surfaces at the time of the R wave peak from a simultaneously recorded ECG.

9 Mitral valve E-F slope<sup>3</sup>. This was measured as the maximal slope of the tangent between the mitral valve E to F points in diastole and was expressed in mm/sec.

Table I Duration of abstinence

| Period             | Number of patients |
|--------------------|--------------------|
| 3 months to 1 year | 9                  |
| 2 to 5 years       | 7                  |
| 6 to 10 years      | 4                  |
| Over 10 years      | ■                  |

Table II Echocardiographic values in adults

|                                      | Normal<br>(13 subjects) |           | Alcoholic<br>(26 subjects) |           |
|--------------------------------------|-------------------------|-----------|----------------------------|-----------|
|                                      | Mean                    | Range     | Mean                       | Range     |
| PW Ex (mm)                           | 12.8                    | 8-22      | 13.6                       | 8-20      |
| Vel (mm/sec)                         | 45.0                    | 30-100    | 50.6                       | 30-80     |
| Thick (mm)                           | 7.2                     | 6-10      | 7.8                        | 7-9       |
| VS Ex (mm)                           | 8.6                     | 5-13      | 7.7                        | 5-12      |
| Vel (mm/sec)                         | 33.9                    | 20-50     | 32.9                       | 20-50     |
| Thick (mm)                           | 9.1                     | 7-11      | 9.4                        | 7-14      |
| ΔS (%)                               | 39                      | 30-59     | 38                         | 21-54     |
| EF (%)                               | 78                      | 66-97     | 75                         | 42-90     |
| V <sub>cf</sub> (circumferences/sec) | 1.18                    | 0.80-1.58 | 1.13                       | 0.40-1.67 |
| PEP/LVET                             | 0.29                    | 0.23-0.36 | 0.31                       | 0.23-0.36 |
| EF slope (mm/sec)                    | 102.0                   | 70-130    | 106.0                      | 75-140    |

Includes only 20 subjects

Abbreviations: PW = left ventricular posterior wall Ex = maximal excursion Vel = maximal systolic velocity Thick = thickness VS = ventricular septum ΔS = % shortening of left ventricular dimension EF = ejection fraction V<sub>cf</sub> = mean velocity of circumferential fiber shortening PEP/LVET = pre-ejection period/left ventricular ejection EF slope = maximal mitral valve EF slope

Table III Echocardiographic values in children

|                            | Normal<br>(8 subjects) |           | Children of alcoholic mothers<br>(7 subjects) |           |
|----------------------------|------------------------|-----------|---|-----------|
|                            | Mean                   | Range     | Mean  | Range     |
| PW Ex (mm)                 | 12.6                   | 7-17      | 10.3  | 8-13      |
| Vel (mm/sec)               | 50.0                   | 35-75     | 41.4  | 30-50     |
| Thick (mm)                 | 7.5                    | 6-8       | 7.6   | 7-8       |
| VS Ex (mm)                 | 6.7                    | 5-9       | 6.9   | 5-10      |
| Vel (mm/sec)               | 33.6                   | 20-50     | 35.0  | 25-50     |
| Thick (mm)                 | 9.0                    | 7-11      | 9.2   | 7-11      |
| ΔS (%)                     | 42                     | 30-48     | 37  | 30-45     |
| EF (%)                     | 80                     | 68-86     | 74  | 66-83     |
| V <sub>cf</sub> (circ/sec) | 1.21                   | 0.82-1.65 | 1.14  | 0.86-1.0  |
| PEP/LVET                   | 0.28                   | 0.25-0.33 | 0.29  | 0.27-0.32 |
| EF slope (mm/sec)          | 108.0                  | 80-130    | 110.0   | 100-125   |

Includes only two subjects

For abbreviations please refer to Table II

## Results

**History physical exam and ECG** None of the 26 alcoholics had evidence on physical examination of cardiac abnormality. Two had mild chronic obstructive pulmonary disease. One individual had a myocardial infarction approximately one year ago but no residual ECG abnormalities. None of the others had ECG abnormalities apart from one adult individual who had congenital complete heart block.

The seven children had no evidence of cardiac abnormality by history, physical examination or ECG.

**Echocardiography** These results are summarized in Tables II and III.

Adequate echograms of the left ventricular cavity (Fig. 3) were obtained in all adult alcoholics and children of alcoholic mothers. The parameters of left ventricular function were found to be normal in all except one adult alcoholic when compared to age-matched controls. This individual was a 41-year-old white male with a 19-year history of alcoholism and a one-year period of abstinence. He had no history of cardiac disease, no cardiovascular symptoms, and his physical examination and ECG were normal. His per cent ΔS (21 per cent), EF (42 per cent), and mean V<sub>cf</sub> (0.40 circumferences/sec) were depressed. His PEP/LVET ratio could not be measured since adequate recordings of the aortic valve were not obtained. One additional adult alcoholic had a slightly thickened ventricular septum (14 mm).

PEP/LVET ratios were obtained in 20 of 26 adult alcoholics and two of the seven children (Figs. 2 and 4). None had an abnormal value.

## Discussion

Alcohol has a direct toxic effect on cardiac musculature.<sup>11</sup> Mitochondrial damage with decreased mitochondrial oxidative enzymes results in diminished energy production and decreased contractility.<sup>12</sup> Changes in sarcoplasmic reticulum appear responsible for impaired excitation-contraction coupling with decreased calcium delivery to the contractile apparatus.<sup>13</sup> Additionally, acetaldehyde, the principal metabolite of ethanol, causes myocardial release of norepinephrine, and this catecholamine depletion may contribute to decreased left ventricular contractility.<sup>14</sup> Although the associated nutritional deficiencies of thiamine and nicotinic acid may occasionally play a role in the cardiovascular disease

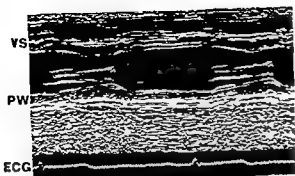


Fig 3 Normal echocardiogram of a left ventricular dimension in a chronic alcoholic patient following a long period of abstinence VS = ventricular septum PW = left ventricular posterior wall ECG = electrocardiogram

of chronic alcoholism<sup>2, 23</sup> the hyperkinetic left ventricular abnormality produced by these states differs greatly from the hypokinetic low cardiac output syndrome associated with the cardiac failure of the chronic alcoholic.<sup>7</sup>

Clinical experiments using normal volunteers and animals have shown transient depression of left ventricular function following acute ingestion of alcohol. This has been demonstrated by cardiac catheterization echocardiography and systolic time intervals measured in the conventional manner.<sup>7</sup> Cardiomyopathy with clinically obvious cardiac decompensation has been documented in chronic alcoholics who had no known evidence for underlying heart disease.<sup>2, 7</sup>

Depression of left ventricular function has also been noted in chronic alcoholics who have had no clinical evidence of cardiac dysfunction.<sup>24</sup> Regan and colleagues<sup>2</sup> studied a group of chronic alcoholic subjects with cardiac catheterization using angiotensin infusion to increase left ventricular afterload. Significant abnormal elevation of left ventricular diastolic pressure as well as decreased left ventricular contractility were noted.

In two separate investigations Spodick and co workers<sup>2</sup> and Wu and associates<sup>25</sup> studied chronic alcoholics who had no cardiac symptoms and found abnormal systolic time intervals indicating left ventricular dysfunction in both groups. Matthews and colleagues<sup>26</sup> utilized echocardiography to evaluate 26 asymptomatic alcoholics and found 81 per cent with thickened left ventricular posterior walls and 30 per cent with decreased mitral EF slopes.

All except one in our study had normal echocardiographic indices of left ventricular function while none had evidence by history, physical

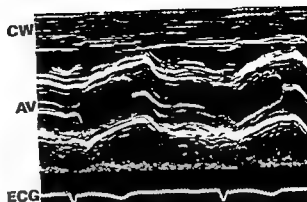


Fig 4 Normal echocardiogram of the aortic root in a chronic alcoholic patient following a long period of abstinence AV = aortic valve CW = chest wall ECG = electrocardiogram

examination or ECG of ventricular dysfunction. The longer period of abstinence of our alcoholic population may account for this difference. The studies of Regan and colleagues<sup>2</sup> were performed after approximately 3 weeks hospitalization and the investigation of Wu and associates<sup>25</sup> was conducted on alcoholics with mean periods of abstinence of only 12 days. The alcoholics in the study by Spodick and co workers<sup>2</sup> were examined 2 to 3 days after their last alcohol ingestion while the alcoholic group of Matthews and colleagues<sup>26</sup> were studied after only a two week minimum interval of abstinence. On the other hand, all our alcoholics had not ingested alcohol for a significantly longer period (mean duration 31 years) (Table I).

The period of active alcoholism in our group appears comparable in duration to that of Regan and associates<sup>2</sup> (at least 10 years), Matthews and co workers<sup>26</sup> (at least 6 years), and Wu and colleagues<sup>25</sup> (average duration of 15 years) while no information regarding this factor was found in the study by Spodick and collaborators.<sup>2</sup>

In view of the left ventricular dysfunction documented by others in chronic asymptomatic alcoholics within a short period of abstinence, it is possible that our population had abnormal left ventricular function when they were actively drinking or earlier in their period of abstinence and later reverted to normal. However, none of our subjects were studied while actively drinking or earlier in their period of abstinence and no data are available regarding the functional status of their left ventricle during that time. No assumptions can thus be made regarding the presence of left ventricular dysfunction in our subjects in the early stages of rehabilitation.



despite the accounts in the literature. Although no longitudinal objective studies have so far been performed in symptomatic alcoholics with cardiac dysfunction, clinically demonstrable improvement of their left ventricular failure has been reported in significant numbers following complete cessation of alcohol consumption.<sup>11-13</sup> Additionally, reversal of alcoholic cardiomyopathy following abstinence from alcohol has been documented by cardiac catheterization and angiography in a single instance.<sup>14</sup>

It has been suggested that alcohol might damage the developing fetus, although direct proof is lacking.<sup>15</sup> Alcohol freely passes the placental barrier and high blood levels have been found in newborn infants comparable to those of their mothers.<sup>16</sup> Alcohol withdrawal syndrome as well as central nervous system depression have been reported in the newborn.<sup>17-19</sup>

In the present investigation only a small number of children with prolonged exposure to alcohol in utero were studied. However, the finding of normal left ventricular parameters in all of them would suggest that alcohol does not affect left ventricular function when these children are assessed by echocardiography after a long interval following exposure to alcohol.

In conclusion, our study demonstrates no clinical or echocardiographic evidence of left ventricular dysfunction in asymptomatic chronic alcoholic adults or in children born of alcoholic mothers when studied following a long period after alcohol exposure. Although it might prove difficult, there is a need for a prospective longitudinal study of chronic alcoholics while they are drinking and serially during the course of their rehabilitation to objectively determine the incidence of left ventricular dysfunction induced by alcohol and its potential reversibility following alcohol withdrawal.

### Summary

Left ventricular function was analyzed using standard echocardiographic techniques in 26 chronic asymptomatic alcoholics without clinical evidence of cardiovascular disease. All were studied following a long period of abstinence (mean 31 years, range 3 months to 17 years). Seven asymptomatic children (mean age 14.1 years, range 4 to 19 years) whose mothers had been actively drinking throughout their pregnancies were also studied. The calculated fractional

shortening of the left ventricle (per cent  $\Delta S$ ), ejection fraction, mean velocity of circumferential fiber shortening (mean  $V_{cf}$ ), excursions and maximal systolic velocities of the ventricular septum and left ventricular posterior wall, pre-ejection period/left ventricular ejection time ratios, mitral valve EF slopes and thicknesses of the left ventricular posterior wall and ventricular septum were obtained in all. Normal left ventricular function was found in all but one adult alcoholic. In this patient, the per cent  $\Delta S$ , ejection fraction, and mean  $V_{cf}$  were reduced. One additional adult alcoholic had a minimally thickened ventricular septum. Our results differ from other studies which have shown significant left ventricular dysfunction in asymptomatic chronic alcoholics. A possible explanation is the much longer period of abstinence of our chronic alcoholics at the time of their examinations. It also appears that left ventricular function in children born of alcoholic mothers is not affected when assessed after the long interval following prolonged exposure to alcohol in utero.

We are indebted to Carl Hatch of the Rochester Mental Health Center and to J. Chandler Terhune for help with this study. We thank Mrs. Summer King for typing the manuscript.

### REFERENCES

1. Pombo J F, Troy B L, and Russell R O. Left ventricular volumes and ejection fraction by echocardiography. *Circulation* 43:480, 1971.
2. Fortuin N J, Hood W P, and Craig E. Evaluation of left ventricular function by echocardiography. *Circulation* 46:26, 1972.
3. Belenkie I, Nutter D O, Clark D W, McGraw D B, and Razner A E. Assessment of left ventricular dimensions and function by echocardiography. *Am J Cardiol* 31:755, 1973.
4. Paraskos J A, Grossman W, Salter S, Dalen J E, and Dexter L. A non-invasive technique for the determination of velocity of circumferential fiber shortening in man. *Circ Res* 29:610, 1971.
5. Ludbrook P, Karlner S J, Peterson K, Leopold G, and O'Rourke R A. Comparison of ultrasound and cine angiographic measurements of left ventricular performance in patients with and without wall motion abnormalities. *Br Heart J* 35:1026, 1973.
6. Ratcheson R A, Boyd C N Jr, Rackley C E, Moraski R E, and Russell R O Jr. Quantitative echocardiography: Correlations with ventricular volumes by angiography in patients with coronary artery disease with and without wall motion abnormalities (Abstr.). *Circulation* 48 (Suppl 1):14, 49, 1973.
7. Redwood D R, Henry W L, and Epstein S E. Evaluation of the ability of echocardiography to measure acute alterations in left ventricular volume. *Circulation* 50:901, 1974.
8. Wessler A M, Harris W S, and Schoenfeld C D.

- Systolic time intervals in heart failure in man *Circulation* 36 149 1968
- 9 Kumar N and Spodick D M Study of the mechanical events of the left ventricle by atraumatic techniques. Comparison of methods of measurement and their significance *AM HEART J* 80 401 1970
  - 10 Vredevoe L A Creekmore E P and Schiller N B The measurement of systolic time intervals by echocardiography *J Clin Ultrasound* 2 99 1974
  - 11 Hirschfeld S Meyer H A and Kaplan S Non invasive right and left systolic time intervals by echocardiography (Abstr.) *Ped Res* 8 350 1974
  - 12 Stefades M A and Witham A C Systolic time intervals by echocardiography *Circulation* 51 114 1975
  - 13 McDonald I G and Hobson E H A comparison of the relative value of non invasive techniques. Echocardiography, systolic time intervals and apexcardiography in the diagnosis of primary myocardial disease *AM HEART J* 84 454 1974
  - 14 Wendt V E Wu C Balcon R Doty G and Bing R J Hemodynamic and metabolic effects of chronic alcoholism in man *Am J Cardiol* 15 145 1965
  - 15 Ferrans V J Alcoholic cardiomyopathy *Am J Med Sci* 252 89 1966
  - 16 James T N and Bear E S Effects of ethanol and acetaldehyde on the heart *AM HEART J* 74 743 1967
  - 17 Wenger N K Myocardial involvement in systemic disease. Ethyl alcohol in The heart Hurst J W ed New York 1974 McGraw-Hill Book Company Inc p 136f
  - 18 Swartz M H Repke D I Katz A M and Rubin E Effects of ethanol on calcium binding and calcium uptake by cardiac microsomes *Biochem Pharmacol* 23 2369 1974
  - 19 Regan T J Levinson G E Oldewurtel H A Martin J F Weiss A B and Moschos C B Ventricular function in non cardiac with alcoholic fatty liver. Role of ethanol in the production of cardiomyopathy *J Clin Invest* 48 397 1969
  - 20 Asokan S K Martin J F and Witham A C Cardio myopathy without cardiomegaly pm alcoholics *AM HEART J* 84 13 1972
  - 21 Spodick D H Pigott V M and Chirife R Preclinical cardiac malfunction in chronic alcoholism *N Engl J Med* 288 6 7 1972
  - 22 Zambrano S S Mazzotta J F Sherman D and Spodick D H Cardiac dysfunction in unselected chronic alcoholic patients. Non invasive screening by systolic time intervals *AM HEART J* 87 318 1974
  - 23 Wu C F Sudhakar M Jafari G Ahmed S S and Regan T J Preclinical cardiomyopathy in chronic alcoholics. A sex difference *AM HEART J* 91 981 1976
  - 24 Matthews E C Henry W L Del Negro A A Fletcher R D Snow J A and Epstein S E Echocardiographic abnormalities in asymptomatic chronic alcoholics (Abstr.) *Clin Res April* 1976 pp 229A
  - 25 Mitchell J H and Cohen L S Alcohol and the heart *Mod Concepts Cardiovasc Dis* 39 109 1970
  - 26 Ahmed E S Levinson G E and Regan T J Depression of myocardial contractility with low doses of ethanol in normal man *Circulation* 48 378 1973
  - 27 Delgado C E Fortuin N J and Ross R S Acute effects of the low dose of alcohol on left ventricular function by echocardiography *Circulation* 51 533 1975
  - 28 Chapman E R and Williams P T Jr Intravenous alcohol as an obstetrical analgesia *Am J Obstet Gynecol* 61 6 6 1951
  - 29 Fogelman A M Abbasi A S Pearce M L and Kattus A A Echocardiographic study of the abnormal motion of the posterior left ventricular wall during angina pectoris *Circulation* 46 905 1972
  - 30 Feigenbaum H Appendix in Echocardiography Philadelphia 1972 Lea & Febiger Publishers pp 215
  - 31 Edler I Ultrasound cardiograms in mitral valve disease *Acta Chir Scand* 111 30 1956
  - 32 Brink A J Lochner A and Lewis C M Thiamine deficiency and beriberi heart disease. Biochemical and clinical investigations, S Afr Med J 40 581 1966
  - 33 Wenger N K Myocardial involvement in systemic disease. Pellagra in The heart Hurst J W ed New York 1974 McGraw-Hill Book Company Inc pp 136i
  - 34 Demaks J G, Proskay A Rahimtoola R H Jamil M Sutton G C Rosen K M Gunner H M and Tobin J R The natural course of alcoholic cardiomyopathy *Ann Intern Med* 80 293 1974
  - 35 Schwartz L Sample K A and Wigle E D Severe alcoholic cardiomyopathy reversed with abstinence from alcohol *Am J Cardiol* 36 963 1975
  - 36 Yaffe S J and Boreus L O Perinatal medicine. Pharmacology in Pediatrics Barnett H L and Einhorn A H eds New York 1977 Appleton Century Crofts/Meredith Corporation pp 55
  - 37 Schaeffer D Alcoholic withdrawal syndrome in a newborn infant of a Yukon Indian mother *Can Med Assoc J* 86 1333 1962
  - 38 Nichol M M Acute alcohol withdrawal syndrome in a newborn *Am J Dis Child* 113 714 1967
  - 39 Grossman M The newborn infant. Physical examination in Pediatrics Barnett H L and Einhorn A H eds New York 1977 Appleton Century Crofts/Meredith Corporation pp 84

# Cardiac abnormalities in cachectic patients before and during nutritional repletion

Steven B Heymsfield, MD  
Robert A Bethel, MD  
Joseph D Ansley, MD  
Daniel M Gibbs, MD  
Joel M Felner, MD  
Donald O Nutter, MD FACP  
Atlanta Ga

Several investigators have studied the effects of protein-calorie undernutrition (PCU) on cardiac structure, size, and function in both man and the experimental animal.<sup>1-4</sup> Although Voit<sup>1</sup> described a normal cardiac weight in protein deficient rats at autopsy and concluded that the heart is spared during starvation,<sup>1</sup> subsequent studies have indicated that cardiac atrophy occurs during inanition. Smythe and colleagues<sup>2</sup> and Wharton and associates<sup>3</sup> observed subnormal cardiac weight in approximately 50 per cent of severely undernourished South African and Ugandan children studied at autopsy. Chauhan and co workers<sup>4</sup> reported that 3 months of a protein deficient diet in the monkey caused a 15 per cent reduction in cardiac weight and microscopic evidence of cardiac atrophy and fibrosis.<sup>4</sup> These animals however experienced a 20 per cent loss in body weight and the microscopic changes in skeletal muscle were more advanced than those in the myocardium. Wharton and colleagues<sup>3</sup> described a diminished radiographic cardiac size in Ugandan kwashiorkor patients and concluded that this was proportional to their loss in body weight. These investigators reported microscopic cardiac

lesions (e.g. vacuolation of myofibrils and fibrosis) at autopsy. Similar pathology however, was present in control patients and Wharton and associates concluded that these lesions were not specific for kwashiorkor. Keys and colleagues<sup>5</sup> observed that in human volunteers exposed to inadequate protein-calorie intake for 6 months the radiographic cardiac size diminished but the decrease in heart volume was only 70 per cent that observed in total body weight.

With regard to cardiac function Edozien and Rahim Khan<sup>6</sup> and Wharton and co workers<sup>3</sup> described normal clinical cardiac status in children with kwashiorkor prior to nutritional therapy. Keys and colleagues<sup>5</sup> and Alleyne<sup>7</sup> on the other hand reported reduced cardiac output in both undernourished adults and in children with kwashiorkor.

While different impressions of cardiac structure and function in the cachectic state have been reported, most investigators have agreed that when such patients are repleted, evidence of circulatory failure frequently occurs. Wharton and colleagues<sup>3</sup>, Keys and co workers<sup>5</sup> and Edozien and Rahim Khan<sup>6</sup> described a progressive increase in radiographic heart size during repletion that was proportionately greater than the gain in body weight. An increase in electrocardiographic (ECG) voltage (Wharton and associates<sup>3</sup>) suggested a parallel enlargement in left ventricular mass. Alleyne<sup>7</sup> and Keys and colleagues<sup>5</sup> also observed progressive augmentation in stroke volume and cardiac output during repletion. In 20 to 30 per cent of Edozien and

From the Departments of Medicine and Surgery, Emory University School of Medicine and Clinical Research Facility, Emory University Hospital, Atlanta, Ga.

Supported by United States Public Health Service Grant RR00079 and by a Grant from the McCandless Fund.

Received for publication May 3, 1978.

Accepted for publication Aug. 16, 1978.

Reprint requests: Steven B. Heymsfield, MD, Clinical Research Facility, Emory University Hospital, Atlanta, Ga. 30322.

Table 1 Clinical history and nutrition data base

| Patient | Age | Sex | Primary diagnosis   | Anthropometric indices |               |       |        | Subnormal laboratory values |
|---------|-----|-----|---|------------------------|---------------|-------|--------|-----------------------------|
|         |     |     |   | % BW                   | % 24 hr cr/ht | % TSF | % MAMC |                             |
| HC      | 52  | F   | Psychogenic anorexia                                      | E <sup>1</sup>         | 54            | 35    | 74     | SCa                         |
| AB      | 56  | F   | Multiple complications from intestinal surgery            | 65                     | 34            | 37    | 56     | SALB HCT RBC FOLATE SCa SZn |
| SF      | 35  | F   | Crohn's disease   | 85                     | 63            | 42    | 15     | SALB HCT SCAR SCa SMg SZn   |
| HG      | 16  | M   | Chronic lymphocytic leukemia                              | 60                     | 35            | 27    | 65     |                             |
| SC      | 32  | M   | Carcinoma   | E <sup>1</sup>         | 38            | 60    | 73     | SALB HCT SCAR SMg SCa       |
| BH      | 48  | F   | Peptic ulcer disease                                      | 55                     | 63            | 30    | 65     | SALB HCT                    |
| WW      | 36  | F   | Psychogenic anorexia                                      | 60                     | 32            | 53    | 58     | SALB HCT RBC FOLATE         |
| PS      | 68  | F   | Whipple procedure for suspected carcinoma of the pancreas | E                      | 57            | 24    | 72     | SALB HCT SCAR               |
| JK      | 68  | M   | Cancer of pancreas  | E                      | 29            | 30    | 10     | SALB HCT                    |
| SCR     | 34  | F   | Cancer of colon   | 16                     | 55            | 29    | 72     | SALB HCT RBC FOLATE SCa     |

24 hr urine creatinine-to-height ratio is an index of lean body mass.

E<sup>1</sup> = edema weight therefore is an unreliable index of weight loss.

Rahim Khans cases signs of congestive heart failure occurred during the first 3 weeks of nutritional repletion (early recovery syndrome). Smythe and co workers and Keys and colleagues also noted cardiac dysfunction (e.g. an enlarged cardiothoracic ratio and a smaller stroke volume and cardiac output compared to pre starvation values) during recovery from protein deprivation in both children and adults.

Three recent developments in nutrition and cardiology have led us to reexamine in the present study cardiac size and function in cachectic patients before and during nutritional repletion. (1) PCU is now common among hospital patients as indicated by a 30 to 40 per cent prevalence in recent surveys of two hospitals in the United States. (2) effective methods for achieving rapid repletion of the cachectic patient by either the central intravenous peripheral intravenous or enteral route have now been developed and are in common use. (3) echocardiography is now available as an accurate non-invasive method for quantitatively describing the anatomic dimensions and functional performance of the heart. In phase A of the present study we utilized echocardiography and other non-invasive

techniques to characterize cardiac size and function in a group of 10 hospitalized patients with severe PCU. In phase B five of these patients were repleted by intravenous or enteral hyperalimentation for a period of 3 to 6 weeks while we continued to monitor clinical status, cardiac size and cardiac function.

#### Methods

**Subjects.** During July to December 1975 12 patients were referred to the Division of Nutrition at Emory University Hospital because of severe PCU as evidenced by these criteria: loss of  $\geq 25$  per cent of body weight (BW) during past 2 years; non edematous BW  $\leq 85$  per cent of ideal midarm muscle circumference (MAMC) and triceps skinfold (TSF) both  $\leq 75$  per cent of standard; and 24 hour urine creatinine to height ratio ( $24 \text{ hr cr/ht}$ )  $\leq 75$  percent of standard.<sup>11</sup> Two patients had a history of heart disease preceding the present wasting illness and were excluded from this study; the remaining 10 form the population for phase A. A clinical description of these patients and selected results that describe their nutritional status are presented in Table 1.

# Cardiac abnormalities in cachectic patients before and during nutritional repletion

Steven B Heymsfield MD

Robert A Bethel, MD

Joseph D Ansley, MD

Daniel M Gibbs, MD

Joel M Felner, MD

Donald O Nutter MD, FACP

Atlanta Ga

Several investigators have studied the effects of protein-calorie undernutrition (PCU) on cardiac structure, size and function in both man and the experimental animal.<sup>1-4</sup> Although Voit<sup>1</sup> described a normal cardiac weight in protein deficient cats at autopsy and concluded that 'the heart is spared during starvation, subsequent studies have indicated that cardiac atrophy occurs during inanition. Smythe and colleagues<sup>2</sup> and Wharton and associates<sup>3</sup> observed subnormal cardiac weight in approximately 50 per cent of severely undernourished South African and Ugandan children studied at autopsy. Chauhan and co workers<sup>4</sup> reported that 3 months of a protein deficient diet in the monkey caused a 15 per cent reduction in cardiac weight and microscopic evidence of cardiac atrophy and fibrosis.<sup>4</sup> These animals however experienced a 20 per cent loss in body weight and the microscopic changes in skeletal muscle were more advanced than those in the myocardium. Wharton and colleagues<sup>3</sup> described a diminished radiographic cardiac size in Ugandan kwashiorkor patients and concluded that this was proportional to their loss in body weight. These investigators reported microscopic cardiac

lesions (e.g., vacuolation of myofibrils and fibrosis) at autopsy. Similar pathology, however, was present in control patients and Wharton and associates concluded that these lesions were not specific for kwashiorkor. Keys and colleagues<sup>5</sup> observed that in human volunteers exposed to inadequate protein-calorie intake for 6 months the radiographic cardiac size diminished but the decrease in heart volume was only 70 per cent that observed in total body weight.

With regard to cardiac function, Edozien and Rahim Khan<sup>6</sup> and Wharton and co workers<sup>3</sup> described normal clinical cardiac status in children with kwashiorkor prior to nutritional therapy. Keys and colleagues<sup>5</sup> and Alleyne<sup>7</sup>, on the other hand reported reduced cardiac output in both undernourished adults and in children with kwashiorkor.

While different impressions of cardiac structure and function in the cachectic state have been reported, most investigators have agreed that when such patients are repleted, evidence of circulatory failure frequently occurs. Wharton and colleagues<sup>3</sup>, Keys and co workers<sup>5</sup> and Edozien and Rahim Khan<sup>6</sup> described a progressive increase in radiographic heart size during repletion that was proportionately greater than the gain in body weight. An increase in electrocardiographic (ECG) voltage (Wharton and associates<sup>3</sup>) suggested a parallel enlargement in left ventricular mass. Alleyne<sup>7</sup> and Keys and colleagues<sup>5</sup> also observed progressive augmentation in stroke volume and cardiac output during repletion. In 20 to 30 per cent of Edozien and

From the Departments of Medicine and Surgery, Emory University School of Medicine and Clinical Research Facility, Emory University Hospital, Atlanta, Ga.

Supported by United States Public Health Service Grant RR00019 and by a Grant from the McCandless Fund.

Received for publication May 3, 1977.

Accepted for publication Aug 16, 1977.

Reprint requests: Steven B Heymsfield MD, Clinical Research Facility, Emory University Hospital, Atlanta, Ga. 30322.

Table II Hyperalimentation protocols for five malnourished patients during phase II

| Patient | Type of HA  | Duration of HA (days) | Daily intake    |                   |          |              |
|---------|---|-----------------------|-----------------|-------------------|----------|--------------|
|         |   |                       | Calories (kcal) | Carbohydrate (Gm) | Fat (Gm) | Protein (Gm) |
| SC      | P <sub>am</sub> + oral feedings                     | 20                    | 2970            | 363               | 122      | 92           |
| BH      | C <sub>am</sub>                                     | 30                    | 3468            | 867               | 11       | 135          |
| WW      | Isocal via NGT                                      | 30                    | 3000            | 375               | 126      | 75           |
| PS      | Vivonex HN via NGT and Intralipid + P <sub>am</sub> | 35                    | 3471            | 487               | 120      | 109          |
| SCR     | Isocal via NGT                                      | 30                    | 3628            | 450               | 151      | 117          |

Intakes of Na, K, Cl, Mg, P, Ca, and Mn were one to three times the recommended daily allowance (RDA). All abbreviations are defined under Methods section.

Table III Radiographic and echocardiographic cardiac dimensions in malnourished patients (Phase A)

| Patient                     | Chest x ray                    |                              | Echocardiogram                 |                   |                            |                   |               |               |              |                            |                             |
|-----------------------------|--------------------------------|------------------------------|--------------------------------|-------------------|----------------------------|-------------------|---------------|---------------|--------------|----------------------------|-----------------------------|
|                             | RHV<br>(cc)                    | RHV/BW<br>(cc/kg)            | EdV<br>(cc)                    | EdV/BW<br>(cc/kg) | EsV<br>(cc)                | EsV/BW<br>(cc/kg) | LVWTd<br>(mm) | LVWTs<br>(mm) | IVSd<br>(mm) | LV mass<br>(Gm)            | LV<br>mass/BW<br>(Gm/kg)    |
| H.C                         | 443                            | 11.5                         | 723                            | 19                | 84                         | 20                | 90            | 160           | 90           | 143                        | 3.7                         |
| A.B                         | 349                            | 11.3                         | 294                            | 10                | 61                         | 20                | 92            | 130           | 100          | 90                         | 2.9                         |
| S.F                         | 409                            | 8.4                          | 871                            | 17                | 11.8                       | 25                | 66            | 118           | 70           | 107                        | 2.1                         |
| H.G                         | 484                            | 12.0                         | 1106                           | 27                | 23.5                       | 60                | 78            | 160           | 71           | 150                        | 3.7                         |
| S.C                         | 515                            | 11.8                         | 645                            | 11                | 9.0                        | 15                | 80            | 185           | 90           | 115                        | 2.0                         |
| B.H                         | 635                            | 17.3                         | 318                            | 8                 | 8.9                        | 24                | 96            | 114           | 54           | 103                        | 2.7                         |
| W.W                         | 330                            | 11.4                         | 711                            | 2.5               | 23.5                       | 60                | 60            | 106           | 48           | 84                         | 2.9                         |
| P.S                         | 619                            | 13.1                         | 680                            | 14                | 13.4                       | 30                | 84            | 118           | 100          | 126                        | 2.7                         |
| J.K.                        | 515                            | 9.3                          | 787                            | 14                | 14.1                       | 25                | 80            | 140           | 90           | 128                        | 2.3                         |
| S.C.R.                      | 416                            | 9.7                          | 679                            | 20                | 29.9                       | 70                | 72            | 140           | 70           | 118                        | 2.7                         |
| Patient<br>mean $\pm$<br>SD | 412 $\pm$<br>107 $\frac{1}{2}$ | 11.3 $\pm$ 2.6 $\frac{1}{2}$ | 696 $\pm$<br>244 $\frac{1}{2}$ | 17 $\pm$ 8        | 14.9 $\pm$ 8 $\frac{1}{2}$ | 4 $\pm$ 2         | 80 $\pm$ 11   | 137 $\pm$ 25  | 79 $\pm$ 19  | 116 $\pm$ 21 $\frac{1}{2}$ | 2.8 $\pm$ 0.7 $\frac{1}{2}$ |
| Control<br>mean $\pm$<br>SD | 634 $\pm$<br>115               | 9.9 $\pm$ 2.2                | 1105 $\pm$<br>223              | 17 $\pm$ 7        | 32.7 $\pm$ 9.7             | 50 $\pm$ 10       | 76 $\pm$ 1.5  | 129 $\pm$ 17  | 80 $\pm$ 2.3 | 149 $\pm$ 100              | 2.3 $\pm$ .5                |
| Control<br>range            | 435-791                        | 8.1-17.2                     | 754-1594                       | 1.3-2             | 19.3-41.2                  | 30-17             | 56-10         | 102-16        | 62-12.3      | 90-247                     | 1.7-3.1                     |

Control values represent mean  $\pm$  SD and range for height and age: matched normal control subjects.  $\dagger = P < 0.01$ ,  $\ddagger = P < 0.05$ ,  $\S = P < 0.01$ .

$\frac{1}{2}$  = P < 0.001 for comparison with controls.

V, volume below or above the control range. All abbreviations are defined under Methods section.

$\frac{1}{2}$  = technically inadequate observation.

day period. Urine, stools, and diet were analyzed for N, P, Na, K, Cl, and Ca.<sup>22</sup> Daily elemental balances (N and P in grams, Na, K, Cl, and Ca in mEq) during each period were calculated as daily intake minus daily output (urine content plus average fecal content).

## Results

**Phase A.** The several different causes of the severe malnutrition that had been present for 6 to

2 years in our patients are shown in Table I. Anthropometric indices and 24 hr cr/hr ratio revealed a marked reduction in lean body mass (LBM) in all 10 patients. Further indications of substandard nutrition included hypoalbuminemia (in eight of 10 patients), anemia (eight out of 10), and subnormal serum levels of carotene (three out of nine), red blood cell folate (three out of eight), magnesium (two of nine), and zinc (two of four). Serum calcium was frequently subnor-

**Nutritional data base** A nutrition data base was completed on each subject and consisted of anthropometric data according to the method of Butterworth and colleagues<sup>13</sup> (height (ht) (cm), BW (Kg), per cent of standard BW TSF MAMC, 24 hr cr /ht), serum proteins (hemoglobin hematocrit (HCT)), prothrombin time, partial thromboplastin time, total iron binding capacity, serum albumin (SALB), total protein, amino acid profile, and serum lipoprotein electrophoresis), minerals (serum levels of Ca (SCa) PO, Mg (SMg), Cu Zn (SZn), Mn Fe and 24 hour urine Zn, Mg, and Cu), and vitamins (serum levels of carotene (SCAR), ascorbic acid thiamine, B<sub>6</sub>, folate and red blood cell (RBC) folate)

**Cardiovascular data base** The cardiovascular evaluation comprised the following studies (1) Complete physical examination, (2) standard 12 lead electrocardiogram (ECG), (3) thyroid function testing (4) standard posterior-anterior and lateral chest x rays Total heart volume was calculated from these films using the method of Keets and Enge<sup>14</sup> where radiographic heart volume (RHV) in ml = (length) × (breadth) × (depth) × (0.42) and (5) echocardiography (echo)

Echocardiograms were performed in the supine position on each subject as previously described<sup>15</sup> In each record five different complexes were analyzed and the data averaged to calculate the following variables<sup>16</sup> Heart rate (beats/minute) (HR) end diastolic and end systolic left ventricular wall thickness (mm) (LVWTD and LVWTS) interventricular septal thickness (mm) (IVSD) diastolic and end systolic left ventricular internal dimensions (mm) (LVIDD and LVIDS) and volumes (cc) (EdV and EsV), left ventricular mass (Gm) (LV mass), stroke volume (cc/beat) (SV), cardiac output (liters/minute) (CO) ejection fraction (EF) mean rate of left ventricular circumferential fiber shortening (circ/sec) (Vcf) per cent systolic thickening of the posterior left ventricular wall (per cent) (PWT), and left ventricular posterior wall excursion (mm) (PWE)

A pericardial effusion (PF) was considered present if an anterior and posterior epicardial to pericardial (P) echo free space was present and pericardial pulsations were absent

The relative change in absolute cardiac dimensions of cachectic patients was established by

matching each phase A patient with a 'reference man or woman of the same height ( $\pm 2$  cm) but of standard weight (100 per cent  $\pm 10$ ) The matched control subjects were healthy, young (age range 19 to 30 years) volunteers in whom the same anthropometric and cardiovascular tests were done as in the undernourished patients The absolute values for radiographic and echocardiographic volumes, mass, and cardiac output in both cachectic patients and matched controls were also normalized for BW Student's *t* test was used to evaluate the statistical significance of differences between the patient and control groups

**Nutritional repletion** Five of the 10 patients were selected for hyperalimentation (HA) on the basis that (1) nutritional repletion was believed to offer an improved prognosis, and (2) the patient agreed to a 2 to 3 month period of hospitalization on the metabolic research ward The cardiovascular data base and selected nutritional indices were determined at weekly intervals for the duration of the patient's hospitalization

HA in the present study was defined as daily nutrition furnishing per day 3 000 to 4 000 Kcal and one to three times the recommended daily allowance (RDA) of all macro and micro nutrients required by man (Table II)

Subjects entering phase B received HA by one or a combination of three routes (Table II) which have been described in earlier reports<sup>10-12</sup> Route 1 is infusion of a polymeric or monomeric liquid diet (Isocal, Vivonex, Vivonex HN) via a thin nasogastric tube (NGT) (No 16 intracath) Route 2 is infusion of a 900 mosmolar nutrient solution (P<sub>900</sub>)<sup>11</sup> or lipid emulsion (intra lipid) via peripheral vein Route 3 is infusion of the 1 800 mosmolar HA solution of Dudrick and colleagues<sup>10</sup> (C<sub>1800</sub>) via central vein (subclavian catheterization) The volume of solution was gradually increased over a several day period to 3 to 4 liters and continued for 2 to 5 weeks at 3 000 to 4 000 Kcal/day The daily intake of calories and nutrients administered to each subject is given in Table II

**Metabolic balance studies** Metabolic balance studies were performed during HA as previously described<sup>17</sup> Urine was collected in 24 hour pools and stools in 3 day pools At the end of each period, the colon was emptied by an enema Daily fecal elemental content was considered as one third of the fecal content for the corresponding 3

Table V Nutritional and cardiac responses to hyperalimentation in five malnourished patients (Phase B)\*

| Variable measured      | Baseline  | Days of hyperalimentation |           |        |
|------------------------|-----------|---------------------------|-----------|--------|
|                        |           | 5-15                      | 20-35     |        |
| BW (Kg)                | 43 ± 11   | 44 ± 10                   | 49 ± 8    | (+12%) |
| 24 hr cr (mg)          | 575 ± 148 | 630 ± 183                 | 679 ± 110 | (28%)  |
| Blood pressure (mm/Hg) | 98/68     | 97/60                     | 98/63     |        |
| RHV (cc)               | 563 ± 109 | 668 ± 232                 | 707 ± 254 | (+25%) |
| EdV (cc)               | 65 ± 20   | 77 ± 19                   | 103 ± 21† | (+59%) |
| LV mass (Gm)           | 109 ± 16  | 126 ± 24‡                 | 143 ± 36  | (+31%) |
| HR (beats/min.)        | 87 ± 15   | 89 ± 10                   | 93 ± 5    | (+13%) |
| SV (cc)                | 47 ± 14   | 57 ± 12                   | 80 ± 18‡  | (68%)  |
| CO (L/min)             | 3.9 ± 1.6 | 5.1 ± 1.5‡                | 7.4 ± 1.4 | (+90%) |
| EF                     | 74 ± 10   | 75 ± 10                   | 72 ± 10   | (-3%)  |
| PF                     | 0/5       | 1/5                       | 2/5       |        |

\* Values represent mean ± SD. BW, body weight; cr, creatinine; P, per cent increase over baseline value. Serial chest x-rays available on three out of five subjects. † P < 0.1; ‡ P < 0.05; § P < 0.01; || P < 0.001 for comparison with baseline. All abbreviations are defined under Methods.

corrected SV and CO were elevated 8 and 25 per cent respectively above control values. Systolic ejection phase indices of left ventricular function viz EF, Vcf, PWE and PWT were normal or in some cases significantly elevated compared to control values. No patient examined in phase A had a pericardial effusion.

**Phase B.** Selected variables that illustrate changes in the nutritional and cardiovascular status of the five patients who received HA are contained in Table V. These data show progressive improvement in BW and lean body mass (24 hr cr excretion) during therapy. BW increased by  $0.3 \pm 0.11$  kilogram/day. In addition, strongly positive metabolic balances were noted for N ( $+10.3 \pm 1.8$  Gm/day), P ( $+0.27 \pm 0.08$  Gm/day), Na ( $+57.8 \pm 15.3$  mEq/day), K ( $+30.5 \pm 10.2$  mEq/day), Cl ( $+54.3 \pm 16.3$  mEq/day), Ca ( $+31.3 \pm 57.8$  mg/day) and Mg ( $+5.1 \pm 5.2$  mEq/day).

The cardiovascular status of these patients also changed during the HA phase. During the first 5 to 15 days of therapy, intracardiac volume expanded rapidly, thus RHV and EdV both increased by 20 per cent over baseline. In contrast, LV mass enlarged by only 15 per cent. Absolute SV and CO also increased during this period by 21 and 31 per cent respectively. The cardiac index increased and exceeded the normal range in three of the five cases. During the next 3 weeks, ventricular volumes, CO and SV continued to increase gradually. In contrast, LV mass

increased only by about 10 per cent of the initial phase A value per week. EF and Vcf remained within the normal range throughout. HR remained unchanged or increased slightly during HA and the initial phase A blood pressures which averaged only 98/68 were stable throughout.

Two patients (W W and B H) developed physical signs and symptoms of congestive heart failure at approximately 20 and 30 days of HA, respectively. Both patients were treated with diuretics. HA was terminated in one and both responded with clearing of signs and symptoms. In the remaining three subjects, no clinical evidence of congestive heart failure was detected.

A pericardial effusion developed on day 20 in two subjects (W W and P S) but in both cases partial resolution occurred by day 30.

The results of phase B studies in one patient are presented here in detail to illustrate the course of HA. Patient W W, a 36-year-old woman with psychogenic anorexia, had lost 60 pounds over an 8-year period. Initial evaluation showed severe PCU (60 per cent of standard BW) with anemia. Absolute RHV, echo EdV, LV mass and CO were 50, 35, 34 and 48 per cent less than corresponding values of her height-matched control subject. When those variables were indexed for BW, however, the values were 33, 34 and 11 per cent greater than the corresponding weight-adjusted values from the matched control. EF and Vcf were decreased by 5 per cent



Table IV Echocardiographic evaluation of left ventricular function in malnourished patients (Phase A)

| Patient              | HR<br>(beats/min) | SV<br>(cc) | SV/BW<br>(cc/kg) | CO<br>(L/min) | CO/BW<br>(L/min/kg) | EF        | Vcf<br>(circ/sec) | PWE<br>(mm) | PWT<br>(%)  |
|----------------------|-------------------|------------|------------------|---------------|---------------------|-----------|-------------------|-------------|-------------|
| HC                   | 77                | 63.9       | 17*              | 4.9           | 13**                | 89*       | 17*               | 130**       | 77.8        |
| AB                   | 86                | 23.3*      | 8                | 2.0*          | 07                  | 79        | 14                | 9.8         | 5*          |
| SF                   | 67                | 70.3       | 14               | 4.7           | 10                  | 86*       | 16*               | 16.0**      | 18.8        |
| HG                   | 119*              | 74.6       | 19**             | 8.9**         | 20**                | 82*       | 16*               | 14.2*       | 105*        |
| SC                   | 90*               | 53.5*      | 9                | 4.8           | 08                  | 83**      | 17**              | 14.5*       | 131.3**     |
| BH                   | 83                | 22.9*      | 6                | 1.9*          | 05*                 | 72        | 13                | 8.4*        | 18.8        |
| WW                   | 63                | 47.6*      | 16**             | 2.9*          | 10                  | 68        | 10                | 9.4*        | 76.7        |
| PS                   | 78                | 54.6*      | 12               | 4.3           | 09                  | 80        | 14                | 12.0**      | 40.5*       |
| JK                   | 60                | 64.6       | 12               | 3.9           | 07                  | 82**      | 17*               | 13.0        | 70          |
| SCR                  | 100*              | 58.0       | 13               | 5.8           | 13**                | 66        | 12                | 10.5        | 97          |
| Patient mean<br>± SD | 82 ± 18.3†        | 53.3 ± 17‡ | 13 ± 4           | 4.4 ± 2       | 10 ± 0.3            | 80 ± 0.8† | 15 ± 2‡           | 12.1 ± 2.5† | 75.3 ± 32   |
| Control mean<br>± SD | 68.3 ± 11         | 77.9 ± 5   | 12 ± 4           | 5.3 ± 1.2     | 08 ± 0.2            | 72 ± 0.4  | 12 ± 2            | 10.5 ± 6    | 70.8 ± 18.9 |
| Control range        | 54-86             | 56.1-112   | 0.9-15           | 3.6-7.1       | 0.6-1               | 63-80     | 0.9-14            | 9.6-11.2    | 51-103      |

Control values represent mean ± SD and range for height and sex matched normal control subjects.

† = P < 0.1 ‡ = P < 0.05 § = P < 0.01 for comparison with controls.

Value below or above control range All abbreviations are defined under Methods section

mal (five of 10), but was proportional to the reduction in serum albumin. None of the five or six patients evaluated for deficiency of thiamine, B<sub>12</sub>, or essential fatty acids had abnormal serum levels of these factors.

The cardiovascular examination demonstrated sinus tachycardia in two subjects and pedal edema in three other individuals. These physical findings were thought to be the result of anemia, hypoalbuminemia and the underlying disease processes rather than manifestations of cardiac dysfunction. There were no other signs of cardiac failure in the phase A patients. The ECG's did not contain significant abnormalities.

RHV data and echo variables describing cardiac dimensions in phase A patients are presented in Table III. Chest x ray examinations revealed a small cardiac silhouette and the calculated RHV in the cachectic group was 37 per cent smaller than in the control group (P < 0.1). However, when RHV was expressed per kilogram of BW, the heart in cachectic subjects was 14 per cent larger (P < 1) than in control subjects. RHV is a combination of two compartments: muscle and fluid (the latter comprising intracardiac chamber volume and the pericardial-epicar-

dial sac). The echocardiogram can determine representative indices of these subcompartments and thereby define their contribution to a small RHV. LVWtd and IVSd measurements did not differ significantly from undernourished and control subjects. When compared to control subjects, echo LV mass in absolute terms was decreased by 22 per cent (P < 0.5), but when expressed per kilogram of BW, LV mass was actually increased by 22 per cent (P < 0.5). Total left ventricular chamber volumes were also decreased,  $\text{mL}$ , EdV by 37 per cent (P < 0.01) and EsV by 54 per cent (P < 0.1). When corrected for BW, EdV was unchanged from control and EsV was decreased by only 26 per cent (NS).

Echo variables describing left ventricular function for patients in phase A are presented in Table IV. HR was 20 per cent faster in malnourished patients (P < 0.1). The absolute SV was decreased by 32 per cent (P < 0.1) and thus absolute CO was depressed by 17 per cent compared to height matched controls. The output values showed considerable variability (e.g. one patient had an elevated output) and the mean CO of the malnourished group did not differ significantly from the control mean. The BW

Table V Nutritional and cardiac responses to hyperalimentation in five malnourished patients (Phase B)\*

| Variable measured      | Baseline  | Days of hyperalimentation |                   |
|------------------------|-----------|---------------------------|-------------------|
|                        |           | 5-15                      | 20-35             |
| BW (kg)                | 43 ± 11   | 44 ± 10                   | 49 ± 8 (+12%)     |
| % hr cr (mg)           | 525 ± 148 | 630 ± 183                 | 672 ± 187‡ (+28%) |
| Blood pressure (mm/Hg) | 98/68     | 97/60                     | 98/63             |
| RHV (cc)               | 563 ± 129 | 668 ± 23°                 | 702 ± 254 (+25%)  |
| EdV (cc)               | 65 ± 20   | 77 ± 19                   | 103 ± 21‡ (+59%)  |
| LV mass (Gm)           | 109 ± 16  | 126 ± 24‡                 | 143 ± 36 (+31%)   |
| HR (beats/min)         | 8° ± 15   | 89 ± 10                   | 93 ± 5 (+13%)     |
| SV (cc)                | 47 ± 14   | 57 ± 12                   | 80 ± 18‡ (+68%)   |
| CO (L/min)             | 3.9 ± 1.5 | 5.1 ± 1.5‡                | 7.4 ± 1.4‡ (+90%) |
| EF                     | 74 ± 07   | 75 ± 08                   | 72 ± 03 (-3%)     |
| PF                     | 0/5       | 1/5                       | 2/5               |

\*Values represent mean ± SD. B charts disclose per cent increase over baseline value. Serial chest x rays available on three out of five subjects. †P < 0.05; ‡P < 0.01; °P < 0.001 for comparison with baseline value. All abbreviations are defined under Method.

corrected SV and CO were elevated 8 and 25 per cent respectively above control values. Systolic ejection phase indices of left ventricular function viz EF, Vcf, PWE and PWT were normal or in some cases significantly elevated compared to control values. No patient examined in phase A had a pericardial effusion.

**Phase B** Selected variables that illustrate changes in the nutritional and cardiovascular status of the five patients who received HA are contained in Table V. These data show progressive improvement in BW and lean body mass (24 hr excretion) during therapy. BW increased by 0.3 ± 0.11 kilogram/day. In addition, strongly positive metabolic balances were noted for N (+10.3 ± 1.8 Gm/day), P (+0.27 ± 0.06 Gm/day), Na (+57.6 ± 15.3 mEq/day), K (+30.5 ± 10.2 mEq/day), Cl (+54.3 ± 16.3 mEq/day), Ca (+31.3 ± 57.8 mg/day) and Mg (+5.1 ± 5.2 mEq/day).

The cardiovascular status of these patients also changed during the HA phase. During the first 5 to 15 days of therapy, intracardiac volume expanded rapidly; thus RHV and EdV both increased by 20 per cent over baseline. In contrast, LV mass enlarged by only 15 per cent. Absolute SV and CO also increased during this period by 21 and 31 per cent respectively. The cardiac index increased and exceeded the normal range in three of the five cases. During the next 3 weeks, ventricular volumes, CO and SV continued to increase gradually. In contrast, LV mass

increased only by about 10 per cent of the initial phase A value per week. EF and Vcf remained within the normal range throughout. HR remained unchanged or increased slightly during HA, and the initial phase A blood pressures which averaged only 98/68 were stable throughout.

Two patients (W W and B H) developed physical signs and symptoms of congestive heart failure at approximately 20 and 30 days of HA respectively. Both patients were treated with diuretics. HA was terminated in one and both responded with clearing of signs and symptoms. In the remaining three subjects, no clinical evidence of congestive heart failure was detected.

A pericardial effusion developed on day 20 in two subjects (W W and P S) but in both cases partial resolution occurred by day 30.

The results of phase B studies in one patient are presented here in detail to illustrate the course of HA. Patient W W, a 36-year-old woman with psychogenic anorexia, had lost 60 pounds over an 8-year period. Initial evaluation showed severe PCU (60 per cent of standard BW) with anemia. Absolute RHV, echo EdV, LV mass and CO were 50, 35, 34 and 48 per cent less than corresponding values of her height-matched control subject. When those variables were indexed for BW, however, the values were 3, 33, 34 and 11 per cent greater than the corresponding weight-adjusted values from the matched control. EF and Vcf were decreased by 5 per cent.

Table IV Echocardiographic evaluation of left ventricular function in malnourished patients (Phase A)

| Patient              | HR<br>(beats/min) | SV<br>(cc)  | SV/BW<br>(cc/kg) | CO<br>(L/min) | CO/BW<br>(L/min/kg) | EF        | Vcf<br>(circ/sec) | PWE<br>(mm) | PWT<br>(%)  |
|----------------------|-------------------|-------------|------------------|---------------|---------------------|-----------|-------------------|-------------|-------------|
| HC                   | 77                | 63.9        | 1.7**            | 4.9           | 1.3*                | 69*       | 1.7**             | 13.0        | .78         |
| A II                 | 86                | 23.3*       | .8               | 2.0*          | .07                 | 79        | 1.4               | 9.8         | .52         |
| SF                   | 67                | 70.3        | 1.4              | 4.7           | 1.0                 | 86*       | 1.6**             | 16.0        | .78         |
| HG                   | 119**             | 74.6        | 1.9*             | 8.9**         | 2.0*                | 82*       | 1.6**             | 14.2**      | 1.05*       |
| SC                   | 90*               | 53.5*       | .9               | 4.8           | .08                 | 83**      | 1.7**             | 14.5        | 1.31*       |
| BH                   | 83                | 22.9*       | .6*              | 1.9           | .05*                | 72        | 1.3               | 8.4*        | 1.85*       |
| WW                   | 60                | 47.6*       | 1.6**            | 2.9*          | 1.0                 | 68        | 1.0               | 9.4*        | .767        |
| PS                   | 78                | 54.6*       | 1.2              | 4.3           | .09                 | 80        | 1.4               | 12.0*       | 4.05*       |
| JK                   | 60                | 64.6        | 1.2              | 3.9           | .07                 | 82**      | 1.7**             | 13.0**      | .75         |
| SCR                  | 100**             | 58.0        | 1.3              | 5.8           | 1.3*                | 66        | 1.2               | 10.5        | .97         |
| Patient mean<br>± SD | 82 ± 18.3†        | 53.3 ± 17.5 | 1.3 ± .4         | 4.4 ± 2       | 1.0 ± .03           | 80 ± .08† | 1.5 ± .2†         | 12.1 ± 2.5† | 75.3 ± 3.2  |
| Control mean<br>± SD | 68.3 ± 11         | 77.9 ± 5    | 1.2 ± .4         | 5.3 ± 1.2     | .08 ± .02           | 72 ± .04  | 1.2 ± .2          | 10.5 ± .6   | 70.8 ± 15.9 |
| Control range        | 54-86             | 56.1-112    | .09-1.5          | 3.5-7.1       | .06-1               | 63-80     | .09-1.4           | 9.6-11.2    | 51-103      |

Control values represent mean ± SD and range for height and sex matched normal control subjects

† =  $P < 0.1$  ‡ =  $P < 0.05$  § =  $P < 0.01$  for comparison with controls

Value below \* or above control range All abbreviations are defined under Methods section

mal (five of 10) but was proportional to the reduction in serum albumin. None of the five or six patients evaluated for deficiency of thiamine  $B_{12}$  or essential fatty acids had abnormal serum levels of these factors.

The cardiovascular examination demonstrated sinus tachycardia in two subjects and pedal edema in three other individuals. These physical findings were thought to be the result of anemia, hypoalbuminemia, and the underlying disease processes rather than manifestations of cardiac dysfunction. There were no other signs of cardiac failure in the phase A patients. The ECG's did not contain significant abnormalities.

RHV data and echo variables describing cardiac dimensions in phase A patients are presented in Table III. Chest x ray examinations revealed a small cardiac silhouette and the calculated RHV in the cachectic group was 37 per cent smaller than in the control group ( $P < .01$ ). However, when RHV was expressed per kilogram of BW, the heart in cachectic subjects was 14 per cent larger ( $P < .1$ ) than in control subjects. RHV is a combination of two compartments: muscle and fluid (the latter comprising intracardiac chamber volume and the pericardial-epicar-

dial sac). The echocardiogram can determine representative indices of these subcompartments and thereby define their contribution to a small RHV. LVWtd and IVSd measurements did not differ significantly from undernourished and control subjects. When compared to control subjects, echo LV mass in absolute terms was decreased by 22 per cent ( $P < .05$ ), but when expressed per kilogram of BW, LV mass was actually increased by 22 per cent ( $P < .05$ ). Total left ventricular chamber volumes were also decreased, e.g., EdV by 37 per cent ( $P < .01$ ) and EsV by 54 per cent ( $P < .01$ ). When corrected for BW, EdV was unchanged from control and EsV was decreased by only 26 per cent (NS).

Echo variables describing left ventricular function for patients in phase A are presented in Table IV. HR was 20 per cent faster in malnourished patients ( $P < .01$ ). The absolute SV was decreased by 32 per cent ( $P < .01$ ) and thus absolute CO was depressed by 17 per cent compared to height matched controls. The output values showed considerable variability (e.g., one patient had an elevated output) and the mean CO of the malnourished group did not differ significantly from the control mean. The BW

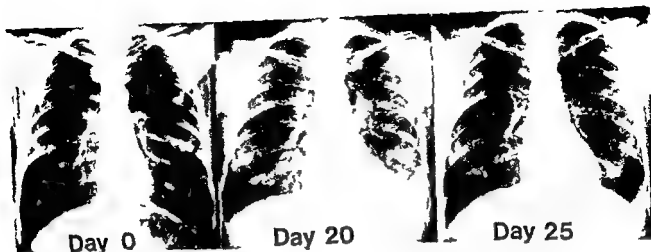


Fig 2 Radiographic changes in patient W W during HA. Note small cardiac silhouette on day 0 pleural effusion and interstitial edema on day 20 the latter abnormalities resolving by day 25. See Fig 1 and text for discussion.

affect the cardiovascular system and this factor should be considered in the interpretation of our results. Secondly, echo has not previously been used to evaluate the hearts of cachectic subjects. The third new aspect was the use of recently developed HA techniques which led to a more rapid reversal of the cachectic state than was previously possible.

Phase A data from our malnourished patients showed that the reduction in heart volume measured both by radiography and echo was proportional to the loss in BW. The echo data indicate that about 60 per cent of this loss in volume represents a reduction in internal chamber volume of the heart and about 40 per cent reduction in cardiac muscle mass. The cardiac mass although sharply reduced had decreased to a lesser degree than the remaining lean body mass i.e. the heart had been partially spared. For example, although the absolute LV mass was approximately 22 per cent smaller than in matched normal subjects, the total BW was diminished by 40 to 45 per cent and consequently the LV mass index was 124 per cent of normal. The reduction in absolute cardiac mass during malnutrition might represent either (1) pathological wasting of myocardium due to impaired protein synthesis or (2) an adaptive response to the reduced blood volume and the reduced CO requirements of the wasted patient. If the loss of cardiac mass is a pathological wasting process, the partial sparing could be related to two interesting features of heart muscle. Cannels and

colleagues<sup>8</sup> showed that rat hearts can maintain protein synthesis by utilizing oxidizable non carbohydrate substances such as fatty acids, ketone bodies, acetate, lactate and pyruvate. This phenomenon is not observed in skeletal muscle. Secondly, Goldberg and co-workers<sup>9</sup> have shown an increase in amino acid uptake and a decrease in protein catabolism in proportion to contractile frequency (and work) in the diaphragm and soleus muscle of rats. If the latter muscle is subjected to an increased workload, an absolute increase in mass will develop even during starvation and negative N balance. The degree of cardiac atrophy in starvation might therefore be the net result of factors diminishing or augmenting cardiac work (i.e. reduced blood pressure, smaller blood volume and hypometabolism versus anemia and hypermetabolism).

Absolute EdV was reduced in our cachectic subjects but was proportional to BW. e.g. EdV/BW was 1.7 in the patients and was also 1.7 in the matched controls. Three conditions present in our patients favored a smaller EdV.

1. EdV is a subcompartment of the plasma volume and might therefore be expected to change in proportion to alterations in the latter. Measurements of plasma volume relative to BW in starving subjects have shown this ratio to increase, remain normal or decrease depending on the severity of disease.<sup>10</sup> Dehydration, diarrhea and vomiting present in some of our subjects would all tend to cause contraction of plasma volume and therefore of EdV.

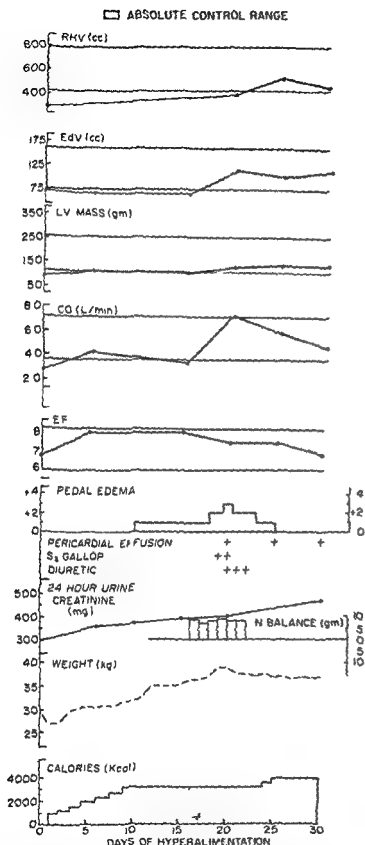


Fig 1 Nutritional and cardiovascular changes during HA in patient W. W. Repletion of lean body mass was demonstrated by positive increments in weight, N Balance, and 24 hr creatinine excretion. Course was uneventful until week 3 when edema, elevated CO, and S<sub>3</sub> gallop required treatment with diuretics. CHF resolved and HA was continued through fourth week. See text for further discussion. All abbreviations are defined under Methods section.

compared to the control subject. Her oxygen consumption was 150 cc/minute. A nasogastric tube (No. 16 intracath) was inserted, and she was given increasing volumes of an Isocal drip (18 hours/day) over a one week interval until the maintenance dose of 3,200 calories/day was reached (Fig 1). Her nutritional course was characterized by steady gain in BW and in lean body mass (reflected in 24 hr creatinine shown in Fig 1) and by strongly positive balances for N, P, K, Na, and Cl. The first 18 days of repletion were uneventful except for the appearance of 1+ pedal edema on day 10. On days 19 and 20, dyspnea, tachycardia, a ventricular diastolic gallop, left pleural effusion, radiographic interstitial pulmonary edema (Fig 2) and pedal edema all appeared. The increase in RHV compared to phase A was shown by echo to be due to three components. LV mass and EdV had both increased 50 to 60 per cent over the pre HA value and a pericardial effusion had developed. The CO and cardiac index compared to the pre HA state had increased by 155 per cent and 90 per cent, respectively. Oxygen consumption had increased by about 30 per cent over the initial value. Ejection phase indices of left ventricular performance remained normal. She was treated with a diuretic (chlorothalidone 50 mg) for 3 consecutive days resulting in weight loss (15 kilograms) and disappearance of dyspnea, tachycardia, edema and the gallop rhythm. Absolute CO returned to the normal range but cardiac index remained elevated. HA was continued for an additional 10 days and the remainder of her hospitalization was uneventful. When the echo obtained after 25 days of HA was compared to the baseline study (Fig 3), a large increase in left ventricular chamber volume and a small pericardial effusion was evident. The pericardial effusion persisted until discharge. LV mass continued to increase and at 4 weeks was only 3 per cent less than that of her height-matched control subject.

## Discussion

The present investigation differs in three respects from previous studies of malnutrition and the heart. First, the patients in this study represent malnutrition secondary to a serious underlying primary disease process. In this group the primary disease process (e.g., cirrhosis, metastatic cancer, and associated severe anemia) may

Consequently cardiac index became further elevated during the first 10 days of HA and remained above normal during the entire course of observation increasing to as much as 250 per cent of baseline in some subjects at 3 to 4 weeks. LV mass index on the other hand remained relatively unchanged throughout the course of HA thus means that repletion of LV mass was proceeding at the same rate as repletion of lean body mass.

The rapid rise of CO and cardiac index could have resulted from two mechanisms that would increase venous return: (1) over expansion of the extracellular fluid compartment and (2) hypermetabolism.

1. Hyperexpansion of the extracellular fluid during HA may arise from either excessive sodium infusion or reduced excretion by the kidney in cachexia. Edozien and Rahim Khan<sup>8</sup> found that milk protein administered to children with PCU in a 5 Gm/kg dose caused expansion of the plasma volume and was associated with congestive heart failure in 20 per cent of these children. When salt and protein were restricted or when diuretics were added to the high protein regimen heart failure became rare. The sodium intake (2 to 4 Gm/day) in our subjects did not appear excessive. Balance ratios (e.g.  $\Delta\text{Na}/\Delta\text{N} = 5.6$ ,  $\Delta\text{Na}/\Delta\text{BW} = 16.7$ ) suggest however that extracellular fluid may have expanded out of proportion to muscle protoplasm as the theoretical values based on repletion of lean body mass with normal composition are 0.77 and 2.6 respectively.<sup>11</sup> Excessive expansion of extracellular fluid during HA could have resulted from subnormal renal excretion of NaCl as described by Alleyne<sup>2</sup> in children with PCU.

2. There is also evidence that a large CO during repletion can result from increased metabolic demands. In both adults and children with malnutrition basal metabolic rate increases rapidly during repletion and sometimes exceeds the normal expected value.<sup>12</sup> In two of our patients in whom basal metabolic rate was measured during HA increases in CO closely paralleled those in metabolic rate.

Two of our five patients developed congestive heart failure during the period of high CO associated with HA while the others remained compensated. Cardiac decompensation under these conditions presumably resulted from a

rapidly expanded plasma volume and augmented metabolic rate which overloaded the small left ventricle. It remains possible that the contractile reserve was also depressed in these hearts. It is unfortunate in this regard that little is known regarding the intrinsic biochemical and ultrastructural disturbances of the myocardium in malnutrition and how these factors may be altered by HA.

### Summary

The effect of PCU and HA on heart dimensions and function was examined with non-invasive methods in 10 patients with severe undernutrition of diverse etiology. Control subjects were 10 normal men and women matched to their cachectic counterparts by height and sex.

The study was conducted in two phases. In phase A baseline studies of heart dimensions and function were completed. Phase B consisted of cardiovascular and metabolic monitoring during 4 to 6 weeks of enteral or parenteral HA.

Phase A was characterized by a reduced radio-graphic total heart volume, echo EDV, LV mass and CO. These reductions however were only one half to one eighth as great as the losses in BW. The patients therefore entered HA with an elevated LV mass index and cardiac index. Ejection phase indices of LV function (EF and Vcf) were normal or enhanced.

Phase B studies in five subjects showed that decreased cardiac size and output were correctable by HA but at differing rates. Ventricular volume and CO corrected more rapidly than LV mass under the conditions of rapid repletion where the daily sodium intake was 2 to 4 grams and values for cardiac index reached 250 per cent of normal. Resting metabolic rate also increased during phase B. The combination of an elevated output, excessive sodium retention and increased metabolic rate while LV mass was still reduced appeared to be responsible for cardiac decompensation in two of five repleted patients.

To prevent cardiac decompensation during the HA of undernourished subjects we propose the use of low salt regimens, a slower rate of HA and serial monitoring of cardiac dimensions and function by clinical examination and echo.

We wish to thank Mr. John Perkins for his assistance with the echocardiograms and Dr. Daniel Rudman for his valuable criticism in preparing this manuscript.

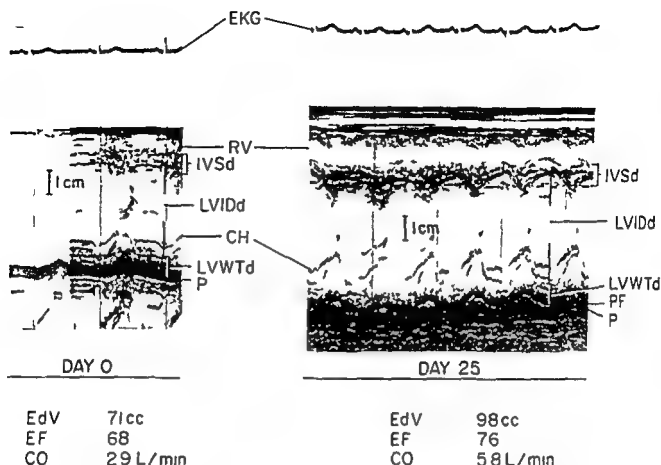


Fig 3 Echo changes in patient W W during HA. Note marked increase in chamber dimensions and calculated CO on day 25 compared to day 0. See Fig 2 for corresponding chest x rays and Fig 1 and text for clinical course. All abbreviations are defined under Methods section.

2. A decreased absolute CO would tend under most conditions to reduce venous return regardless of blood volume size.

3. Also tending to reduce EdV was a 20 per cent faster HR in the cachectic than in the control subjects.

We have also demonstrated that absolute CO was reduced in the malnourished patients. This reduction was less than the reduction in lean body mass and therefore resulted in an elevated cardiac index. Furthermore, indices of ventricular function were normal or enhanced, suggesting that a relative hyperdynamic circulatory state was present. This is in contrast to uncomplicated starvation, where CO and EF have been reported to be depressed.<sup>3,7</sup> Several conditions would tend to promote an increased cardiac index and cardiac work in our patients with nosocomial protein-calorie starvation, e.g., anemia in eight, liver disease in one, and the possibility of cancer hypermetabolism in three.<sup>20</sup> An alternative explanation for the enhanced ventricular function indices is based on the requirement for ventricular shortening to

be maintained or increased in order to maintain SV as ventricular EdV is decreased. EdV fell by 37 per cent whereas SV fell by 32 per cent in our patients. This suggests that EF and shortening indices would have to be preserved or actually increase to produce the observed SV. Myocardial contractile state could not be directly assessed in the present study of intact patients, but the normal or augmented values for Vcf in the presence of normal systemic arterial blood pressure suggests that contractility was not depressed.

During HA, the reductions in LV mass, EdV, and CO were all repaired, but at different rates. Intracardiac volume and CO increased promptly and were largely corrected within 2 weeks. On the other hand, LV mass increased relatively slowly. The absolute level of EdV and CO had returned to the control range by 1 to 2 weeks, whereas LV mass showed only a small change over this period and after 5 to 6 weeks was still below the normal range. BW was also repaired slowly, at a rate of about +5 per cent of initial BW per week.

Consequently cardiac index became further elevated during the first 10 days of HA and remained above normal during the entire course of observation increasing to as much as 250 per cent of baseline in some subjects at 3 to 4 weeks. LV mass index on the other hand remained relatively unchanged throughout the course of HA this means that repletion of LV mass was proceeding at the same rate as repletion of lean body mass.

The rapid rise of CO and cardiac index could have resulted from two mechanisms that would increase venous return: (1) over expansion of the extracellular fluid compartment and (2) hypermetabolism.

1 Hyperexpansion of the extracellular fluid during HA may arise from either excessive sodium infusion or reduced excretion by the kidney in cachexia. Edozien and Rahim Khan<sup>6</sup> found that milk protein administered to children with PCU in a 5 Gm/Kg dose caused expansion of the plasma volume and was associated with congestive heart failure in 20 per cent of these children. When salt and protein were restricted or when diuretics were added to the high protein regimen heart failure became rare. The sodium intake (2 to 4 Gm/day) in our subjects did not appear excessive. Balance ratios (e.g.  $\Delta\text{Na}/\Delta\text{N} = 5.6$ ,  $\Delta\text{Na}/\Delta\text{BW} = 16.7$ ) suggest however that extracellular fluid may have expanded out of proportion to muscle protoplasm as the theoretical values based on repletion of lean body mass with normal composition are 0.77 and 2.6 respectively.<sup>7</sup> Excessive expansion of extracellular fluid during HA could have resulted from subnormal renal excretion of NaCl as described by Alleyne in children with PCU.

2 There is also evidence that a large CO during repletion can result from increased metabolic demands. In both adults and children with malnutrition basal metabolic rate increases rapidly during repletion and sometimes exceeds the normal expected value.<sup>8,9</sup> In two of our patients in whom basal metabolic rate was measured during HA increases in CO closely paralleled those in metabolic rate.

Two of our five patients developed congestive heart failure during the period of high CO associated with HA while the others remained compensated. Cardiac decompensation under these conditions presumably resulted from a

rapidly expanded plasma volume and augmented metabolic rate which overloaded the small left ventricle. It remains possible that the contractile reserve was also depressed in these hearts. It is unfortunate in this regard that little is known regarding the intrinsic biochemical and ultrastructural disturbances of the myocardium in malnutrition and how these factors may be altered by HA.

### Summary

The effect of PCU and HA on heart dimensions and function was examined with non invasive methods in 10 patients with severe undernutrition of diverse etiology. Control subjects were 10 normal men and women matched to their cachectic counterparts by height and sex.

The study was conducted in two phases. In phase A baseline studies of heart dimensions and function were completed. Phase B consisted of cardiovascular and metabolic monitoring during 4 to 8 weeks of enteral or parenteral HA.

Phase A was characterized by a reduced radiographic total heart volume, echo EDV, LV mass and CO. These reductions however were only one half to one eighth as great as the losses in BW. The patients therefore entered HA with an elevated LV mass index and cardiac index. Ejection phase indices of LV function (EF and Vcf) were normal or enhanced.

Phase B studies in five subjects showed that decreased cardiac size and output were correctable by HA but at differing rates. Ventricular volume and CO corrected more rapidly than LV mass under the conditions of rapid repletion where the daily sodium intake was 2 to 4 grams and values for cardiac index reached 250 per cent of normal. Resting metabolic rate also increased during phase B. The combination of an elevated output, excessive sodium retention and increased metabolic rate while LV mass was still reduced appeared to be responsible for cardiac decompensation in two of five repleted patients.

To prevent cardiac decompensation during the HA of undernourished subjects we propose the use of low salt regimens, a slower rate of HA and serial monitoring of cardiac dimensions and function by clinical examination and echo.

We wish to thank Mr. John Perkins for his assistance with the echocardiograms and Dr. Daniel Rudman for his valuable criticism in preparing this manuscript.



# REFERENCES

- 1 Voit C Über die verschiedenheiten der Erweisszersetzung beim Hungern *Z Biol* 2 309 1866
- 2 Smythe P M Swanepoel A and Campbell J A II The heart in kwashiorkor, *Br Med J* 1 67 1962
- 3 Wharton B A Balmer S F Somers K et al The myocardium in kwashiorkor *Q J Med* 149 107 1969
- 4 Chauhan S Nayak N C and Ramalingaswami V The heart and skeletal muscle in experimental protein malnutrition *J Pathol Bacteriol* 90 301, 1965
- 5 Keys A Henschel A and Taylor H L The size and function of the human heart at rest in semi starvation and in subsequent rehabilitation *Am J Physiol* 60 153 1947
- 6 Edozien J C and Rahim Khan M A Anaemia in protein malnutrition *Clin Sci* 34 315 1968
- 7 Alleyne G A O Cardiac function in severely malnourished Jamaican children *Clin Sci* 30 553 1966
- 8 Leevy C M Card L Frank O et al Incidence and significance of hypovitaminemia in a randomly selected municipal hospital population *Am J Clin Nutr* 17 259 1965
- 9 Bistran B H Blackburn G L Hallowell E et al Protein status of general surgical patients *JAMA* 230 858 1974
- 10 Dudrick S J Wilmore D W Vars H M et al Long term parenteral nutrition with growth development and positive nitrogen balance *Surgery* 64 134 1968
- 11 Issacs J Millikan J Stackhouse J et al Parenteral nutrition of adults with a 900 milliosmolar solution via peripheral veins *Am J Clin Nutr* 30 552 1977
- 12 Rhes J W Ghazzawi O and Weidman W Nasojejunal feeding An improved device and intubation technique *J Pediatr* 82 931 1973
- 13 Butterworth C and Blackburn G L Hospital malnutrition and how to assess the nutritional status of a patient a monograph from Nutrition Today Incorporated Annapolis MD 21404
- 14 Keets T E and Enge I P Cardiac mensuration by the cardiac volume method *Radiology* 85 850 1965
- 15 Heymsfield S McNish T Perkins J et al Sequence of cardiac changes in Duchenne muscular dystrophy *Am Heart J* (In press)
- 16 Feigenbaum H Echocardiography Philadelphia 1976, Lea & Febiger 312 pp
- 17 Rudman D Millikan J, Richardson R J et al Elemental balances during intravenous hyperalimentation of underweight adult subjects *J Clin Invest* 55 94 1975
- 18 Cannells D E Hyalmarson A C and Morgan H E Effects of non carbohydrate substrate on protein synthesis in muscle *Am J Physiol* 226 528 1974
- 19 Goldberg A L Biochemical events during hypertrophy of skeletal muscle in Cardiac Hypertrophy Ed Alpert N H New York 1971 Academic Press Inc pp 301 314
- 20 Gennenger L D and Mider G B Energy and nitrogen metabolism in cancer *Adv Cancer Res* 2 229 1954
- 21 Reutenstein E C Jr Allbright F., and Wells S L The accumulation interpretation and presentation of data pertaining to metabolic balances notably those of calcium phosphorus and nitrogen *J Clin Endocrinol Metab* 5 367 1945
- 22 Alleyne G A O The effects of severe protein calorie malnutrition on the renal function of Jamaican children *Pediatrics* 39 400 1967
- 23 Keys A Brozak J Wenschel A et al In The Biology of Human Starvation, vol 1 Minneapolis 1950 Minnesota Press p 303
- 24 Montgomery R D Changes in the basal metabolic rate of the malnourished infant and their relation to body composition *J Clin Invest* 41 1653 1962

## Hemodynamic evaluation of the Ionescu-Shiley pericardial xenograft in the mitral position

Anand P Tandon MD MRCP

Donald R Smith MD FRCP

Marian I Ionescu MD FACS

Leeds England

Glutaraldehyde treated pericardial xenografts have been used for heart valve replacement during the past 6 years. Clinical results have been extremely gratifying. Very low thrombogenicity without anticoagulant therapy is one of the important benefits of this type of valve replacement. This report presents the results of a late hemodynamic evaluation of 27 patients and of sequential studies of six patients who had mitral valve replacement with the Ionescu Shiley pericardial xenograft.\*

### Patients and methods

Since March 1971 106 patients had mitral valve replacement with pericardial xenografts. Actuarial survival and event free curves are shown in Fig 1. Four embolic episodes were noted in the entire series. All were mild or trivial, occurred within the first 6 weeks following valve replacement and left no sequelae. Clinically 94 per cent of patients were in Grade I (NYHA) at the latest assessment.

Twenty seven patients underwent hemodynamic evaluation at a mean duration of  $40.3 \pm 2.8$  (range 24 to 59) months following valve insertion. The criteria for selection were an interval of at least two years from valve replacement and the informed consent of the patient.

From the Departments of Cardiology and Cardiothoracic Surgery, The General Infirmary, Leeds, England.

Received for publication June 19, 1977.

Accepted for publication March 16, 1978.

Reprint requests: M. I. Ionescu, M.D., Department of Cardiothoracic Surgery, The General Infirmary, Leeds LS1 3EX, England.

\*Shiley Laboratories, Irvine, California.

The annulus diameter of the grafts used was 25 mm in two patients, 27 mm in 15 patients and 29 mm in 10 patients. The clinical details of these patients are shown in Table I. Six patients had in addition to the preoperative investigation two separate hemodynamic studies performed at mean intervals of  $11.2 (\pm 1.6)$  and  $42.8 (\pm 3.3)$  months following pericardial xenograft implantation. Of the 20 patients who had preoperative cardiac catheterization, 10 had resting pulmonary artery systolic pressure greater than 60 mm Hg.

All patients were hospitalized 24 hours prior to hemodynamic study. On admission a detailed clinical history, estimation of functional capability, physical examination, hematological assessment, a chest radiograph, a 12 lead electrocardiogram and a phonocardiogram were obtained in all patients. Electrocardiograms and chest radiographs were analyzed for rhythm, left ventricular voltage (using the sum of SV and RV<sub>1</sub>) and cardiothoracic ratio. Right and left heart catheterization was performed in the postabsorptive state without any prior sedation. Pulmonary and systemic pressures were transduced by strain gauge manometers (SEM 486) with the zero level set 5 cm below the sternal angle, integrated electronically and recorded on a multi-channel ultraviolet light recorder (SEM\* 3012). Cardiac output was measured by the direct Fick method using 2 minutes of gas collection. Hemodynamic data were obtained during a 4 minute period of rest and between the fourth and sixth minute of a 6-minute period of supine leg exercise on a bicycle.

Sheila and Epstein Monitoring, Middlesex, U.K.

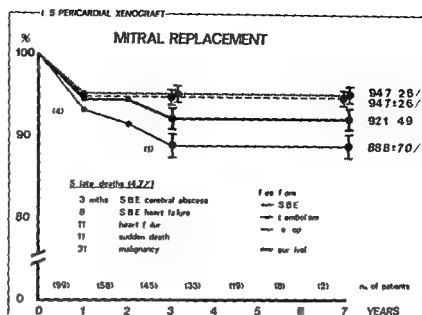


Fig 1 Actuarial analysis of results following mitral pericardial xenograft valve replacement. The data are expressed as per cent expected survival rate and individual event free curves for complications.

Table 1 Preoperative clinical details

|                                  | Number of patients        |
|----------------------------------|---------------------------|
| Male                             | 8                         |
| Female                           | 19                        |
| Age                              |                           |
| Mean                             | 43.6 yrs<br>( $\pm 1.8$ ) |
| Range                            | 19-62 yrs                 |
| Clinical lesion                  |                           |
| Stenosis                         | 9                         |
| Incompetence                     | 8                         |
| Mixed                            | 12                        |
| Rhythm                           |                           |
| Atrial fibrillation              | 19                        |
| Sinus rhythm                     | 8                         |
| Functional status (NYHA)         |                           |
| II                               | 6                         |
| III                              | 19                        |
| IV                               | 2                         |
| Previous closed mitral valvotomy | 12                        |

ergometer. Left ventricular angiograms were performed in all patients at the end of the study.

Pulmonary vascular resistance was calculated using the standard formula. The mean diastolic gradient across the pericardial xenograft was measured by planimetric integration of at least five simultaneously recorded phasic left ventricular and pulmonary wedge tracings. The xeno-

graft surface area was calculated according to the hydraulic formula of Gorlin and Gorlin.

## Results

### Electrocardiographic and radiological changes

The mean cardiothoracic ratio showed a significant decrease from a preoperative level of 0.59 to 0.54 at the postoperative study ( $p < 0.001$ ). The mean left ventricular voltage was 34.8 mm preoperatively and 33.8 mm at the postoperative study. This difference was not statistically significant.

**Hemodynamic findings at rest** The results are given in Tables II and III.

The mean cardiac index showed a significant increase from a preoperative level of  $1.9 \text{ L/min/M}^2$  to  $2.6 \text{ L/min/M}^2$  at the postoperative study ( $p < 0.001$ ). The oxygen uptake also showed a smaller but still significant rise ( $p < 0.05$ ). The mean pulmonary artery and wedge pressures were significantly reduced at the postoperative study ( $p < 0.001$ ) with a corresponding reduction in mean pulmonary vascular resistance ( $p < 0.01$ ). Postoperatively, the mean diastolic gradient across the xenograft was  $6.4 (\pm 0.5) \text{ mm Hg}$  and the calculated xenograft surface area was  $2.0 (\pm 0.1) \text{ cm}^2$ . The results obtained in 10 patients with severe preoperative pulmonary hypertension are presented in Table III. This group of patients showed reductions in mean pulmonary artery and wedge pressures and in pulmonary

Table II Pre and postoperative hemodynamic data (Mean values  $\pm$  SEM) of 27 patients with pericardial xenografts in the mitral position

|         | O uptake<br>(ml/min/M) |           | Cardiac index<br>(L/min/M) |          | PWP<br>(mm Hg) |          | PAP<br>(mm Hg) |          | PVR<br>(dynes sec cm M) |            | Mean diastolic gradient<br>(mm Hg) |          | Calculated xenograft surface area (cm) |          |
|---------|------------------------|-----------|----------------------------|----------|----------------|----------|----------------|----------|-------------------------|------------|------------------------------------|----------|--|----------|
|         | R                      | E         | R                          | E        | R              | F        | R              | E        | R                       | E          | R                                  | E        | R                                      | E        |
| Preop   | 1237                   | 3146      | 19                         | 30       | 233            | 404      | 387            | 571      | 5356                    | 6568       | -                                  | -        | -                                      | -        |
|         | $\pm 60$               | $\pm 404$ | $\pm 01$                   | $\pm 03$ | $\pm 19$       | $\pm 27$ | $\pm 41$       | $\pm 49$ | $\pm 1133$              | $\pm 2411$ | -                                  | -        | -                                      | -        |
| Postop  | 1363                   | 4065      | 26                         | 41       | 138            | 294      | 228            | 490      | 2850                    | 9603       | 64                                 | 153      | 20                                     | 23       |
|         | $\pm 40$               | $\pm 144$ | $\pm 01$                   | $\pm 02$ | $\pm 08$       | $\pm 15$ | $\pm 10$       | $\pm 19$ | $\pm 207$               | $\pm 253$  | $\pm 05$                           | $\pm 09$ | $\pm 01$                               | $\pm 01$ |
| p value | $<0.05$                | $<0.05$   | $<0.001$                   | $<0.01$  | $<0.001$       | $<0.01$  | $<0.001$       | $<0.01$  | $<0.01$                 | $<0.05$    |                                    |          |  |          |

Abbreviations SEM = standard error of the mean PWP = mean pulmonary wedge pressure PAP = mean pulmonary artery pressure  
PVR = pulmonary vascular resistance R = rest E = exercise

Table III Hemodynamic data in 10 patients with preoperative resting pulmonary systolic pressure  $> 60$  mm Hg (Mean values  $\pm$  SEM)

|         | O uptake<br>(ml/min/M) |           | Cardiac index<br>(L/min/M) |          | PWP<br>(mm Hg) |          | PAP<br>(mm Hg) |          | PVR<br>(dynes sec cm M) |            |
|---------|------------------------|-----------|----------------------------|----------|----------------|----------|----------------|----------|-------------------------|------------|
|         | R                      | E         | R                          | E        | R              | E        | R              | E        | R                       | E          |
| Preop   | 1126                   | 3085      | 19                         | 28       | 277            | 445      | 504            | 663      | 5948                    | 834        |
|         | $\pm 59$               | $\pm 501$ | $\pm 09$                   | $\pm 05$ | $\pm 29$       | $\pm 22$ | $\pm 62$       | $\pm 59$ | $\pm 1837$              | $\pm 2398$ |
| Postop  | 1377                   | 3936      | 27                         | 43       | 156            | 298      | 252            | 44       | 2945                    | 989        |
|         | $\pm 77$               | $\pm 193$ | $\pm 02$                   | $\pm 03$ | $\pm 12$       | $\pm 27$ | $\pm 18$       | $\pm 39$ | $\pm 307$               | $\pm 552$  |
| p value | $<0.05$                | $<0.05$   | $<0.01$                    | $<0.01$  | $<0.001$       | $<0.01$  | $<0.001$       | $<0.01$  | $<0.01$                 | $<0.01$    |

Preoperative exercise data in 10 patients only  
Abbreviations SEM = standard error of the mean PWP = mean pulmonary wedge pressure PAP = mean pulmonary artery pressure  
PVR = pulmonary vascular resistance R = rest E = exercise

vascular resistance comparable to those found in patients with a lesser degree of pulmonary hypertension. Thus in this series the severity of preexisting pulmonary hypertension did not seem to influence the postoperative hemodynamic improvement.

**Hemodynamic findings on exercise.** The cardiac index increased significantly from a preoperative level of  $30 \text{ L/min/M}^2$  to  $41 \text{ L/min/M}^2$  postoperatively ( $p < 0.01$ ). For each milliliter increase in oxygen uptake the cardiac index rose  $5.6 \text{ ml}$ . The mean pulmonary artery and wedge pressures showed significant reduction ( $p < 0.01$ ) from the preoperative values, but were still abnormally elevated. The pulmonary vascular resistance also showed significant reduction from the preoperative level ( $p < 0.05$ ). These patients with severe pulmonary hypertension preoperatively showed a similar improvement in

cardiac output, pulmonary pressures and vascular resistance. Mean diastolic gradient increased from a resting value of  $6.4 \text{ mm Hg}$  to  $15.3 \text{ mm Hg}$  on exercise. The calculated surface area showed an increase with exercise to  $2.3 \text{ cm}^2$ .

**Sequential studies.** One preoperative and two separate postoperative studies were performed in six patients. These hemodynamic investigations were carried out under identical physiological conditions and the results are presented graphically in Figs 2 and 3. At the first postoperative study the cardiac index, mean pulmonary artery and wedge pressures and pulmonary vascular resistance showed a significant improvement both at rest and on exercise when compared with the preoperative data. The improvement was similar to that obtained in the entire group of patients as described in the previous paragraphs.

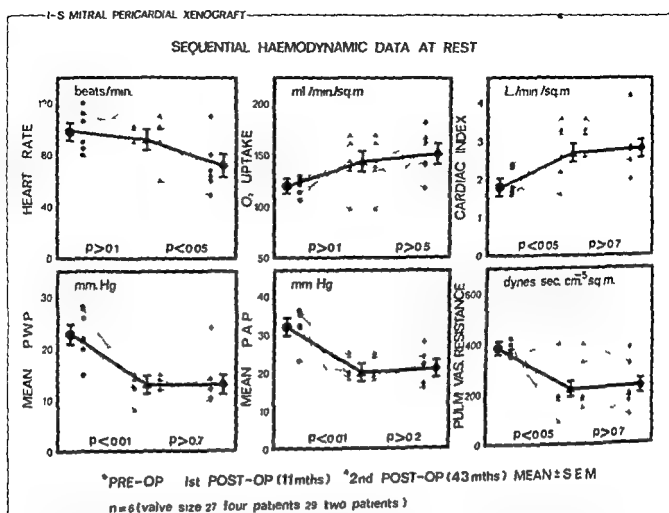


Fig 2 Sequential hemodynamic data at rest from six patients with mitral pericardial xenograft. Mean PWP = mean pulmonary wedge pressure. O Uptake = oxygen uptake. Mean PAP = mean pulmonary artery pressure. Pulm Vasc Resistance = pulmonary vascular resistance. SEM = standard error of the mean.

There were no significant changes in cardiac index, pulmonary artery and wedge pressures and pulmonary vascular resistance between the first and the second postoperative study.

The mean diastolic gradient across the xenografts were 7.1 mm Hg at rest and 20.1 mm Hg on exercise at the first and 6.6 mm Hg and 19.1 mm Hg at the second postoperative study. This difference was not significant. The calculated xenograft areas were 2.2 cm<sup>2</sup> at rest and 2.6 cm<sup>2</sup> on exercise at the first postoperative study. A marginal increase to 2.3 and 2.7 cm<sup>2</sup>, respectively, was noted at the second postoperative study, but again the difference was not significant.

**Left ventricular angiography** Left ventricular angiograms demonstrated competent pericardial xenografts in all patients.

## Discussion

The pericardial xenograft was primarily created to minimize the rate of thromboembolism

traditionally associated with prosthetic replacement of the mitral valve. The experience during the past 6 years has demonstrated that, even without the use of anticoagulants, this aim has been attained. The structural integrity of the xenograft has been maintained as shown by six years of clinical follow up and by over seven years of fatigue testing in vitro.

The results of this study demonstrated that mitral valve replacement with pericardial xenografts produced significant hemodynamic improvement and that this improvement was maintained for periods of up to 59 months following valve insertion. The study also confirmed the previously reported reversibility of pulmonary hypertension following mitral valve replacement.<sup>2,4</sup>

The results showed that although a postoperative increase in cardiac output and in oxygen uptake was demonstrated both at rest and during exercise, the hemodynamic response to exercise

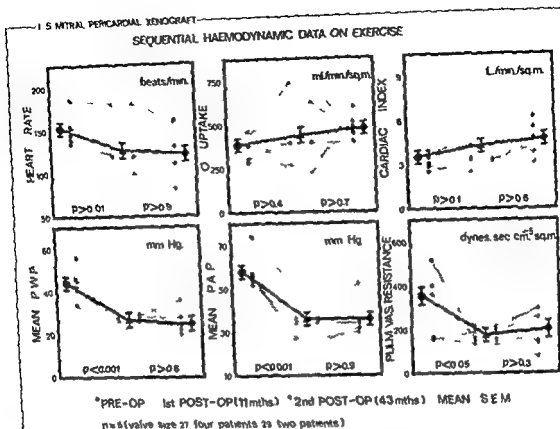


Fig 3 Sequential hemodynamic data on exercise from six patients with mitral pericardial xenograft. Abbreviations as in Fig 2

was still unpaired. Postoperatively the mean pulmonary artery and wedge pressures approached normal figures at rest but rose to abnormal levels with exercise. This seems to be a universal finding with all types of mitral valve replacement<sup>3</sup> and it may be related to the fact that all valve substitutes inserted in the mitral position produce some degree of obstruction to forward flow, especially during exercise. The mean diastolic gradient across the mitral pericardial xenograft of 64 mm Hg compares favorably with gradients obtained with other mitral valve substitutes.

Published results of postoperative hemodynamic evaluations of other currently used mitral valve replacements are given in Table IV. These data provide only a perspective against which the results of the present study can be considered. Direct comparison between results obtained with various valve substitutes is difficult due to the differences in the methods of study and the diversity of patient population. Furthermore, only scanty reports of late hemodynamic eval-

uations are available; the majority of these having been performed at less than 18 months postoperatively as compared with 40 months in the present study. Nevertheless, the data presented in Table IV show that hemodynamically the pericardial xenograft compares favorably with other types of valve substitute used in the mitral position.

Although the number of patients with sequential hemodynamic investigations was small, the results are of considerable importance. They established that maximum circulatory improvement was obtained by the end of the first year following valve insertion and that the functional integrity of the xenograft was maintained intact with the passage of time. Similar results were obtained from investigations performed on patients with pericardial xenografts in the aortic position.<sup>7</sup>

In conclusion, this study has demonstrated significant hemodynamic improvement following mitral valve replacement with the Ionescu-Shiley pericardial xenograft and maintenance of valve

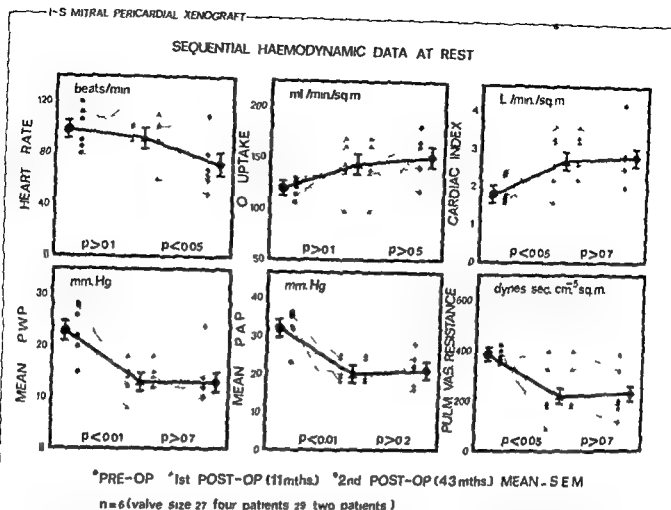


Fig 2 Sequential hemodynamic data at rest from six patients with mitral pericardial xenograft Mean PWP = mean pulmonary wedge pressure O<sub>2</sub> Uptake = oxygen uptake Mean PAP = mean pulmonary artery pressure Pulm Vase Resistance = pulmonary vascular resistance SEM = standard error of the mean

There were no significant changes in cardiac index pulmonary artery and wedge pressures, and pulmonary vascular resistance between the first and the second postoperative study

The mean diastolic gradient across the xenografts were 7.1 mm Hg at rest and 20.1 mm Hg on exercise at the first and 6.6 mm Hg and 19.1 mm Hg at the second postoperative study. This difference was not significant. The calculated xenograft areas were 2.3 cm<sup>2</sup> at rest and 2.6 cm<sup>2</sup> on exercise at the first postoperative study. A marginal increase to 2.3 and 2.7 cm<sup>2</sup> respectively, was noted at the second postoperative study, but again the difference was not significant.

**Left ventricular angiography** Left ventricular angiograms demonstrated competent pericardial xenografts in all patients.

## Discussion

The pericardial xenograft was primarily created to minimize the rate of thromboembolism

traditionally associated with prosthetic replacement of the mitral valve. The experience during the past 6 years has demonstrated that even without the use of anticoagulants this aim has been attained. The structural integrity of the xenograft has been maintained, as shown by six years of clinical follow up and by over seven years of fatigue testing in vitro.

The results of this study demonstrated that mitral valve replacement with pericardial xenografts produced significant hemodynamic improvement, and that this improvement was maintained for periods of up to 59 months following valve insertion. The study also confirmed the previously reported reversibility of pulmonary hypertension following mitral valve replacement.<sup>3,4</sup>

The results showed that although a postoperative increase in cardiac output and in oxygen uptake was demonstrated both at rest and during exercise the hemodynamic response to exercise

- 9 Reid J R, Stevens T W, Segwast W, Fulwider R C and Alexander J L. Hemodynamic evaluation of the Beall mitral valve prosthesis. *Circulation* 45(Suppl. I) 1 1972
- 10 Fernandez J, Morse D, Spagna P, Lemole G, Gooch A, Yang S H and Maranhao B. Results of mitral valve replacement with the Beall prosthesis in 209 patients. *J Thorac Cardiovasc Surg* 71:18 19 1974
- 11 Bjork V O, Book H and Holmgren A. The Bjork Shiley mitral valve prosthesis. *Ann Thorac Surg* 18:39 1974
- 12 Sigwart U, Schmidt H, Gleichmann U and Borst H G. In vivo evaluation of the Lillehei-Kaster heart valve prosthesis. *Ann Thorac Surg* 22:213 1976
- 13 Johnson A M, Daily P O, Peterson K L, LeWinter M, DiDonna G J, Blair G and Niwayama G. Functional evaluation of the porcine heterograft in the mitral position. *Circulation* 52(Suppl. I) 40 1975
- 14 Iune A J, Miller R R, Maxwell K, Vismara L A, Hurley E J and Mason D T. Postoperative hemodynamic assessment of the glutaraldehyde preserved porcine heterograft in the aortic and mitral positions (Abstr). *Circulation* 53 and 54 (Suppl. II) 148 1976
- 15 Book K. Mitral valve replacement with Bjork Shiley tilting disc valve—A clinical and hemodynamic study in patients with isolated mitral valve lesions. *Scand J Thorac Cardiovasc Surg Suppl* 12:2 1974
- 16 Hultgren H, Hubis H and Shumway N E. Cardiac functions following mitral valve replacement. *Am Heart J* 75:302, 1968
- 17 Tandon A P, Smith, R, Whitaker W., and Jonescu M I. Long term haemodynamic evaluation of the aortic pericardial xenograft. *Br Heart J* (In press)



**Table IV** Hemodynamic results following mitral valve replacement with different types of valve substitutes

| Authors                           | Mitral valve substitute        | Time of study (months postop) | Cardiac index (L/min/M <sup>2</sup> ) |      | Mean PWP (mm Hg) |      | Mean diastolic gradient (mm Hg) |      |
|-----------------------------------|--------------------------------|-------------------------------|---------------------------------------|------|------------------|------|---------------------------------|------|
|                                   |                                |                               | R                                     | E    | R                | E    | R                               | E    |
| Pietras et al <sup>1</sup> (1974) | Starr Edwards valve Model 6300 | 163                           | 32                                    | 48   | 13.2             | 30   | 11.6                            | 9.5  |
| Haerten et al (1976)              | Starr Edwards valve Model 6300 | 12                            | 20                                    | 34   | 14               | 26   | 7.2                             |      |
| Bjork et al (1974)                | Bjork Shiley valve—            |                               |                                       |      |                  |      |                                 |      |
|                                   | 50° angle                      | 5 13*                         | 4.6†                                  | 7.4† | 16.7             | 30.4 | 4.3                             | 11.7 |
|                                   | 60° angle                      | 5 13                          | 4.4†                                  | 7.9† | 16.9             | 25.8 | 4.7                             | 8.4  |
| Haerten et al (1976)              | Lillehei Kaster valve          |                               | 20                                    | 34   | 14               | 29   | 6.2                             |      |
| Sigwart et al <sup>2</sup> (1976) | Lillehei Kaster valve          | 1 6*                          | 30                                    |      | 16               |      | 9                               |      |
| Johnson et al (1975)              | Hancock porcine xenograft      | 5 5                           | 26                                    |      | 17               |      | 6.5                             |      |
| Lurie et al <sup>3</sup> (1976)   | Hancock porcine xenograft      | 1 15*                         | 2.5                                   |      | 15               |      | 8                               |      |
| Present study                     | IS pericardial xenograft       | 40.3                          | 2.6                                   | 4.1  | 13.8             | 29.4 | 6.4                             | 15.3 |

Mean period not available

†Cardiac output

Abbreviations PWP = pulmonary wedge pressure R = rest E = exercise

function up to 59 months postoperatively Repeat circulatory investigations will be performed at longer intervals in order to continually appraise the function of this valve

### Summary

Hemodynamic studies were performed in 27 patients at a mean interval of 40.3 (range 24 to 59) months following mitral valve replacement with pericardial xenografts Six patients had sequential studies one before operation and two separate investigations at mean intervals of 11.2 and 42.8 months following valve replacement

The results showed significant increase in cardiac index reduction in mean pulmonary artery and wedge pressures and decrease in pulmonary vascular resistance both at rest and during exercise when compared with the preoperative values The mean diastolic gradient across the pericardial xenografts was 6.4 mm Hg at rest and 15.3 mm Hg during exercise The calculated xenograft surface area was 20 and 23 cm<sup>2</sup>, respectively

The sequential studies established that the maximum hemodynamic improvement was achieved within the first year following valve replacement and that the functional performance of the xenografts was maintained unaltered with the passage of time

We wish to thank Miss Anne E Tunnicliffe for help in the preparation of this manuscript

### REFERENCES

- 1 Ionescu M I Tandon A P Mary D A S and Abid A Heart valve replacement with the Ionescu Shiley pericardial xenograft *J Thorac Cardiovasc Surg* 73 31 1977
- 2 Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve other cardiac valves and central circulatory shunts *Am Heart J* 41 1 1951
- 3 Pietras R J Long D M and Rosen K M Late postoperative clinical and hemodynamic assessment of the early cloth covered Starr Edwards mitral valve prosthesis *J Thorac Cardiovasc Surg* 67 450 1974
- 4 Dillen J M Matloff J M Evans G L Hoppin F G Jr Bhargava P Harken D E and Dexter L Early reduction of pulmonary vascular resistance after mitral valve replacement *N Engl J Med* 277 387 1972
- 5 Zener J C Hancock E W Shumway N E and Harrison D C Regression of extreme pulmonary hypertension after mitral valve surgery *Am J Cardiol* 30 820 1972
- 6 Saul T K Baum W H Jones J V Lommer A R, Thomson R M Turner M A and Escarot A Mitral valve replacement in the presence of severe pulmonary hypertension *Thorax* 31 332 1976
- 7 Russell T H Kremkau E L Kloster F and Starr A Late hemodynamic function of cloth covered Starr Edwards valve prostheses *Circulation* 45 and 46 (Suppl 1) 8 1972
- 8 Haerten K Both A Loogen F and Bracks W Hemodynamics after mitral valve replacement with Starr Edwards Bjork Shiley and Lillehei Kaster prostheses (Abstract) *Circulation* 53 and 54 (Suppl 1) 181 1976

associates<sup>24</sup> After taking the preparations the subjects were given a light standardized breakfast. The same parameters were then registered again 30 minutes later and thereafter at hourly intervals throughout an observation period of five hours. In addition after 1, 2 and 5 hours exertion tests of five minutes duration were performed on the bicycle ergometer at the previously determined individual workloads. During exercise and during the recovery phase the ECG was monitored continuously on a direct writer.

Starting 30 minutes before the administration of the preparations continuous ECG recordings were made over an average period of 5½ hours on a single channel battery powered portable tape recorder (Holter Avionics Model 400 Electrocardiometer). The self adhesive electrodes were fixed on the midclavicular line at the fifth right intercostal space on the manubrium sterni and in the V (exploratory electrode) position. The running speed of the recorder was checked to make sure that there were no fluctuations. The ECG tapes were scanned on an Avionics Model 650 Electrocardioscanner at 60 times the recording speed. Any significant morphological alterations appearing on the oscilloscope and any abrupt changes in heart rate were examined at normal speed and simultaneously traced out for detailed analysis at a paper speed of 25 mm/sec.

In a second series of tests C 50 005/A Ba was given in a dose of 15 mg thrice daily on two consecutive days to four young volunteers aged 23 to 27 years (average 25 years) and the effects were compared with those observed after the administration of placebo on a previous occasion. ECG tracings were recorded continuously for nine hours daily. The subjects were instructed to pursue their normal everyday activities throughout the study.

The statistical significance of the differences between any changes observed after placebo and those produced by the test substance was determined by the t test and is indicated in the figures by  $p < 0.05$   $p < 0.01$  and  $p < 0.001$ . All the values quoted are means with the corresponding standard errors ( $\bar{x} \pm s$ ).

## Results

### Effects of single oral doses

**Heart rate (Fig 1)** Thirty and 60 minutes after the administration of C 50 005/A Ba there was a dose related increase in heart rate of 11 to 20

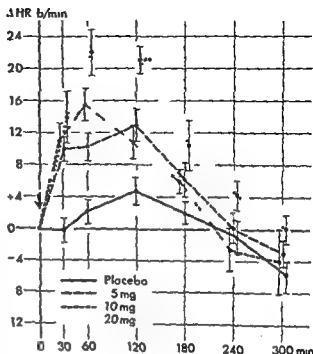


Fig 1 Changes in heart rate after single oral doses of C 50 005/A Ba ( $n = 8$ )

beats/minute above the placebo value. The differences were statistically significant at all dose levels up to 120 minutes after administration. The effects of doses of 5 and 10 mg C 50 005/A Ba remained demonstrable for three hours and that of 20 mg for four hours. There was no statistically significant difference between the results observed in the two age groups.

**Arterial blood pressure (Fig 2)** The effect of C 50 005/A Ba on systolic pressure differed in the two age groups. A dose related increase occurred in both but the values 30 and 60 minutes after administration at all dose levels were distinctly higher in the younger than in the older subjects (18 to 31 as against 4 to 21 mm Hg). The increases in systolic pressure 30 minutes after the administration of the drug were all statistically significant except at the 15 mg dose level in the older group.

The effect of C 50 005/A Ba on diastolic pressure also differed in the two age groups. At all dose levels there was a more marked decrease in the younger group.

The maximum effect on systolic pressure was observed after 30 minutes except at doses of 5 mg in the elder and 20 mg in the younger group. The duration of effect was two hours after a dose of 5 mg and in the younger subjects up to four hours

# Human pharmacology studies with a new, orally active stimulant of cardiac adrenergic beta-receptors

M Knaus MD  
B Pfister MD  
U C Dubach, MD  
P R Imhof MD  
Basel Switzerland

In the management of heart failure substances that stimulate predominantly the adrenergic  $\beta$ -receptors could be of value as an alternative to, or in combination with, cardiac glycosides and could open up a new therapeutic approach. Such drugs should have a positively inotropic effect without causing any significant acceleration of heart rate. They should not induce arrhythmias, and to be widely applicable they would have to be available in both oral and parenteral dosage forms. The relatively cardioselective  $\beta$ -receptor stimulant dobutamine,\* though only administrable by intravenous infusion, is the first compound of this type that appears to produce beneficial effects under clinical conditions.<sup>2, 11, 16</sup>

In investigations in animals a new experimental compound code numbered C 50 005/A Ba or H 80/62† proved to be a cardioselective  $\beta$ -receptor stimulant satisfying the above conditions.<sup>2, 9</sup> In man also it seems to be a selective beta 1 adrenoceptor agonist, which is in addition active by the oral route.<sup>10</sup> The results of human pharmacology studies conducted with this preparation including information on the incidence

and dependence on dosage of disturbances of cardiac rhythm, are described in the present paper.

## Methods

Eight male volunteers free of cardiovascular disorders, who had given their informed consent to the study in writing, each received C 50 005/A Ba in 5 mg tablets in doses of 5, 10 and 20 mg and a placebo, single blind and in random sequence at intervals of one week.

To make allowance for the known difference in the incidence of effort induced arrhythmias due to age<sup>11</sup> the subjects were divided into two groups, one consisting of the four younger subjects aged between 23 and 26 years (average  $24 \pm 0.6$  years) and the other of the elder subjects, whose ages ranged from 49 to 55 years (average  $52 \pm 1.5$  years).

In preliminary tests on a bicycle ergometer (Elema Schonander EM 369) the individual workloads producing an increase in heart rate of 160 beats/minute in the younger group and 140 beats/minute in the elder group were determined. These figures correspond to about 80 per cent of the maximum attainable heart rates in the respective age groups.<sup>11</sup> In the morning before the preparations were taken, recordings were made of heart rate and the ECG and blood pressure was measured by the cuff method after the subjects had lain quietly for 15 minutes. The ECG tracing, carotid pulse wave and phonocardiogram were recorded simultaneously on a three channel writer (Cardiopan 3 T Type 703 Philips Zurich) for subsequent evaluation of the systolic time intervals according to the method of Weissler and

From the Research Department Pharmaceuticals Division CIBA GEIGY Ltd and the Department of Internal Medicine University of Basel Medical Policlinic Cantonal Hospital Basel Switzerland

Received for publication Mar 19 1977

Accepted for publication May 9 1977

Reprint requests Dr U C Dubach Department of Internal Medicine University of Basel Medical Policlinic Cantonal Hospital Basel Switzerland

E Lilly Research Laboratories Indianapolis Ind DL-34-dihydroxy N [3 (4 hydroxyphenyl) 1 methyl n propyl] phenethylamine hydrochloride

\*CIBA GEIGY Ltd Basel Switzerland C 50 005/A Ba AB Hassle Molndal H 80/62† isopropylamino-3 (p hydroxy phenoxy) 2 propanol of hydrochloride hereunder referred to as C 50 005/A Ba

of 5 mg the frequency of marked SAR increased slightly during the observation period of on the average 5½ hours after 10 mg the average for all subjects rose from 81 (placebo and 5 mg) to 102 (n.s.) and after 20 mg to 149 ( $p < 0.05$ ). In three subjects however the occurrence of marked SAR after the various doses of C 50 005/A Ba was no more frequent than after placebo and in some instances even less so. In general not only the frequency of SARs increased but also their intensity since there was a dose related acceleration of the basic heart rate and such abrupt bradycardic phases resulted in extreme fluctuations of sinus rhythm by up to almost 50 beats/minute. Between the second and fourth hours after the administration of C 50 005/A Ba but also after placebo SARs tended to be slightly more frequent otherwise they were fairly regularly distributed throughout the observation period. In particular their occurrence did not specifically coincide with the maximum effect of the drug.

In four subjects transient sinus arrest lasting for 11 to 14 seconds was observed on one or two occasions with subsequent slowing of rhythm and unchanged QRS complexes. In one case this phenomenon only occurred after placebo in the other three it was noted once after 5 mg C 50 005/A Ba twice after 10 mg and once after 20 mg.

Changes in the ST segment were visible in the ECG of one 50 year old subject whose tracings both at rest and during effort had been normal before treatment. Twenty five minutes after a dose of 20 mg C 50 005/A Ba depressions of the ST segments by more than 1 mm appeared unaccompanied by any corresponding clinical symptomatology. As can be seen in Fig 5 there was a correlation between the extent of the ST depression and that of the rise in heart rate and systolic blood pressure.

#### Effects of repeated administration

Continuous ECG recordings (Table II) The changes in cardiac rhythm observed in four healthy young volunteers after 15 mg three times a day of C 50 005/A Ba and placebo on two consecutive days are indicated in Table II. The ECG tracings recorded continuously for an average of nine hours daily showed isolated SVES in all four subjects after the placebo. On the first day of treatment with C 50 005/A Ba SVES were only seen in two subjects but on the second day

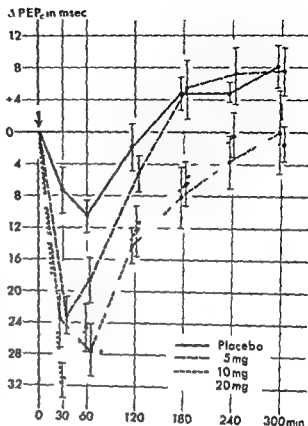


Fig 3 Changes in rate corrected pre-ejection period (PLP) after single oral doses of C 50 005/A Ba ( $n = 8$ )

they were again present in all four. No alterations due to treatment could be established. VES did not occur after placebo medication and altogether only four were seen on the two consecutive days of treatment with C 50 005/A Ba.

The frequency of marked SAR increased on the first day of treatment with C 50 005/A Ba and diminished again on the second. They tended to occur more often during the first hour after the first dose on the first day. None of the above mentioned changes was statistically significant.

Subjective tolerability. Single doses of C 50 005/A Ba were subjectively well tolerated. Fifteen to 20 minutes after doses of 10 mg and 20 mg six of the eight subjects experienced palpitations which usually disappeared within an hour. One of the younger subjects also had a feeling of tightness in the chest and slight headaches at all dose levels.

On the first day of repeated administration two of the four subjects felt slight palpitations 15 minutes after taking C 50 005/A Ba. No other undesirable effects were reported.

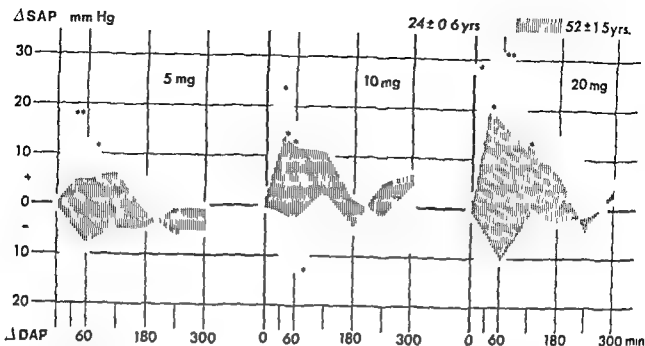


Fig 2 Changes in systolic and diastolic blood pressure in younger and elderly subjects after single oral doses of C 50 005/A Ba ( $n = 8$ )

after 20 mg. The maximum effect on diastolic pressure was noted between 30 and 60 minutes after medication. The decrease was slight and not dose related, and by comparison with the placebo values only significant at one determination each after 5 mg ( $p < 0.05$ ) and 10 mg ( $p < 0.01$ ). The duration of effect was 2 to 3 hours.

**Pre ejection period (PEP) (Fig 3)** The changes in the rate corrected pre ejection period (PEP) which serves as an index of myocardial contractility were not significantly different in the two age groups. An increase in contractility reflected in a distinct decrease of approximately 10 msec in the duration of the PEP, and attributable to digestion was observed after placebo medication. Thirty minutes after the administration of C 50 005/A Ba there was a dose related decrease in PEP. In relation to the placebo values, the reductions recorded after 5, 10 and 20 mg, respectively were  $-16.9$  msec ( $p < 0.05$ ),  $-17.3$  msec ( $p < 0.01$ ), and  $-24.3$  msec ( $p < 0.001$ ), the corresponding 60 minute values were  $-8$  msec ( $n.s$ ),  $-17$  msec ( $p < 0.01$ ) and  $-14$  msec ( $p < 0.05$ ). Up to three hours after doses of 10 and 20 mg the reductions were significantly ( $p < 0.05$ ) different from the placebo values. The maximum increase in contractility was reached 30 minutes after 5 and 20 mg and 60 minutes after 10 mg and the duration of this effect after 10 and 20 mg was three hours.

**Continuous ECG recordings (Figs 4 and 5 Table I)** In each of two of the eight subjects, in

whom the ECG was recorded continuously over an average period of  $5\frac{3}{4}$  hours one ventricular extrasystole (VES) was seen during the first exercise test after placebo medication. After the administration of C 50 005/A Ba there was an on the whole slight non dose related and statistically non significant increase in the frequency of VES, in five of the eight subjects altogether 11 VES occurred—five in three subjects after 5 mg, one in each of three subjects after 10 mg and one in each of three subjects after 20 mg. Of the total of 11 VES recorded after the administration of the drug only two occurred during effort.

**Supraventricular extrasystoles (SVES)** were not observed after placebo but altogether 17 appeared in five subjects after C 50 005/A Ba (seven after 5 mg, seven after 10 mg and three after 20 mg). Scrutiny of the ECG's revealed the combined occurrence of SVES and VES in half of the tracings. Only one of the 17 SVES arose during effort.

**Sinus arrhythmias (SAR)** with changes in pulse rate of more than 30 beats/minute within 4 seconds were recorded in seven of the eight subjects after placebo. These changes were mainly observed in the younger group and were in some cases associated with a considerable slowing of sinus rhythm, independently of respiration and without any conspicuous alteration in the P wave. Prior to the change, heart rate was usually relatively fast ( $> 90$  beats/minute). After the administration of C 50 005/A Ba except in a dose

Table I Occurrence of arrhythmias during an observation period of 5½ hours after single oral doses of C 50 005/A Ba and placebo (n = 8)

| Subj No | Activity                           | Placebo |     |     |    | 5 mg |     |     |    | 10 mg |     |     |    | 20 mg |     |     |    |
|---------|------------------------------------|---------|-----|-----|----|------|-----|-----|----|-------|-----|-----|----|-------|-----|-----|----|
|         |                                    | SVES    | VES | SAR | SA | SVES | VES | SAR | SA | SVES  | VES | SAR | SA | SVES  | VES | SAR | SA |
| 197     | Everyday activity during ergometry |         |     | 3   |    |      |     |     |    |       |     | 5   |    | 2     |     | 10  |    |
| 200     | Everyday activity during ergometry |         |     | 30  |    |      |     | 18  |    |       |     | 32  | 1  |       |     |     | 7  |
| 220     | Everyday activity during ergometry |         |     | 18  |    |      | 3   | 20  | 1  |       | 1   | 20  | 1  |       | 1   |     | 25 |
| 226     | Everyday activity during ergometry |         |     | 14  | 1  | 2    |     | 12  |    | 1     | 1   | 8   |    |       |     |     | 14 |
| 167     | Everyday activity during ergometry |         |     | 7   |    | 2    | 1   | 8   |    |       |     | 1   |    | 1     |     |     | 10 |
| 197     | Everyday activity during ergometry |         |     | 2   |    | 3    |     | 9   |    | 4     | 1   | 10  |    |       | 1   |     | 21 |
| 197     | Everyday activity during ergometry |         | 1   |     |    |      | 1   |     |    | 1     |     |     |    |       |     |     | 1  |
| 197     | Everyday activity during ergometry |         |     |     |    |      |     |     |    | 1     |     | 10  |    |       |     |     | 7  |
| 224     | Everyday activity during ergometry |         | 1   |     |    |      |     |     |    |       |     | 15  |    |       |     | 3   | 1  |
|         | Total                              | 2       | 81  | 1   | 7  | 5    | 78  | 1   | 7  | 3     | 102 | 2   | 3  | 3     | 147 | 1   |    |

p &lt; 0.05

Abbreviations: SVES = supraventricular extrasystoles VES = ventricular extrasystoles SAR = sinus arrhythmias SA = sinus arrest

## Discussion

Stimulation of the cardiac adrenergic  $\beta$  receptors leads to an increase in heart rate and myocardial contractility. If the cardiostimulation is not accompanied with peripheral vasodilatation there is an increase in systolic blood pressure which through the intervention of the baroreceptors checks the acceleration of heart rate. This is certainly one reason why the increase in heart rate following the administration of dobutamine<sup>9</sup> and also C 50 005/A Ba is generally fairly moderate. A further explanation could be that there are—as various authors have postulated<sup>1-3</sup>—two different types of cardiac  $\beta$  receptor of which one predominantly mediates chronotropic and the other inotropic effects. There would accordingly be  $\beta$  stimulants and  $\beta$  blockers that preferentially act on the one or the other type of receptor. Evidence has in fact been adduced suggesting that this is true of certain  $\beta$  blockers.

One as it were unexpected by-product of this study was the finding that the susceptibility of the cardiac adrenergic  $\beta$  receptors to stimulation diminishes with age as manifested by the smaller increase in systolic blood pressure noted in the older subjects. No such difference due to aging was however detectable in the increase in heart rate which in the case of preparations like C

Table II Occurrence of arrhythmias during an observation period of 1½ hours daily on two consecutive days after 15 mg t.i.d. C 50 005/A Ba and placebo (n = 4)

| Subj No | Placebo |     |     | Day 1 |     |     | Day 2 |     |     |
|---------|---------|-----|-----|-------|-----|-----|-------|-----|-----|
|         | SVES    | VES | SAR | SVES  | VES | SAR | SVES  | VES | SAR |
| 197     | 1       |     | 4   | 1     |     | 14  | 3     |     | 1   |
| 200     | 1       |     | 10  |       |     | 58  | 2     |     | 33  |
| 220     | 1       |     |     | 2     |     | 28  | 2     | 1   | 5   |
| 226     | 7       |     | 11  | 1     |     | 11  |       |     | 11  |
| Total   | 10      |     | 25  | 3     | 3   | 109 | 12    | 1   | 53  |

Abbreviations: SVES = supraventricular extrasystoles VES = ventricular extrasystoles SAR = sinus arrhythmias

50 005/A Ba is of course also mediated by the  $\beta$  receptors. This can be attributed to the loss of sensitivity of the baroreceptors with advancing age<sup>4</sup> as a result of which the restraint on the increase in heart rate following the rise in systolic pressure was less marked in the older subjects than in the younger subjects. Hence no difference in the increase in heart rate in the two groups was seen for reasons not directly connected with cardiac function. Whether the diminished susceptibility to  $\beta$  stimulation is caused by a loss of sensitivity or a decrease in the density of

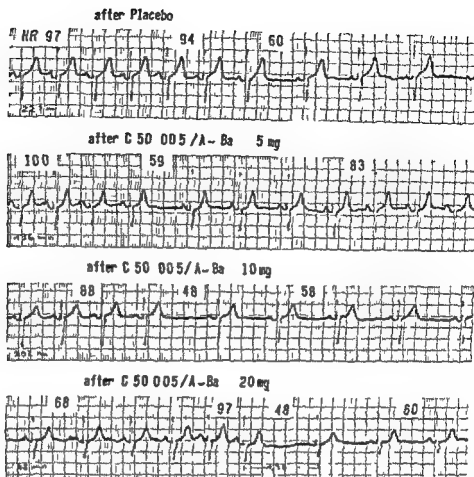


Fig 4 Accentuation of sinus arrhythmia by single oral doses of C 50 005/A Ba in one healthy volunteer

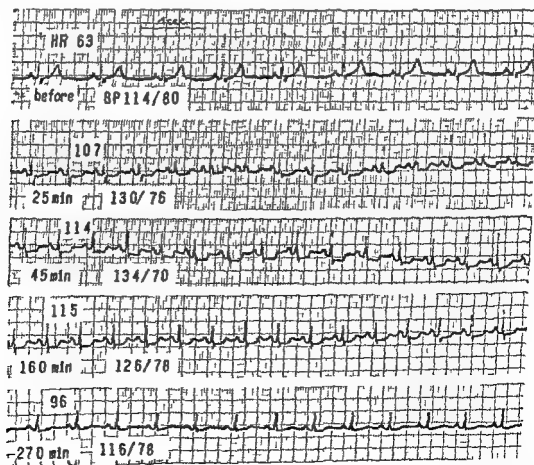


Fig 5 Depression of ST segment in a 50 year old subject after a single oral dose of 20 mg C 50 005/A Ba

with diminished pumping efficiency of the heart due to reduced myocardial contractility (power failure). In patients with coronary disease however it is possible that it might increase myocardial oxygen requirement to a potentially dangerous degree. The compound could presumably also afford a means of counteracting the cardiac effects of  $\beta$  receptor blockade in the event of undesired reactions such as acute heart failure during therapy with  $\beta$  blockers. It could likewise prove beneficial in cases of delayed atrioventricular conduction. The elaboration of a simple test of coronary function with the aid of this preparation lies entirely within the bounds of possibility.

### Summary

The effects of single oral doses of 5, 10 and 20 mg of a new cardioselective  $\beta$  stimulant preparation C 50 005/A Ba were tested and compared with the response to placebo in eight healthy volunteers (four aged 23 to 26 years and four aged 49 to 55 years). The compound induced a dose-related increase in myocardial contractility (reduction of 17 to 24 msec in PEP) and in heart rate which was accelerated by 8 to 20 beats/minute by comparison with the placebo values. The rise in systolic pressure observed in response to C 50 005/A Ba was both dose-related and dependent on the age of the subjects: in the younger group there was an increase of 16 to 31 mm Hg and in the older group an increase of 7 to 21 mm Hg. A slight decrease in diastolic pressure was noted which was likewise more prominent in the younger subjects. These changes were ascribed to a decrease due to aging in the responsiveness of the adrenergic  $\beta$  receptors to stimulation. The effects of the compound set in quickly, reached their maximum within 30 to 60 minutes and persisted for about 4 hours. The only side effects observed were slight palpitations. Depression of the ST segment was noted in one 55 year old subject and was interpreted as a manifestation of latent coronary disease. In view of this finding it seems possible that the preparation could be used as a diagnostic agent for a simple test of coronary function. Continuous ECG recordings over a period of 5½ hours including three ergometer tests at submaximum effort showed that by comparison with placebo C 50 005/A Ba caused a slight increase in the frequency of isolated ventricular and supraventricular premature contractions and also in the incidence and intensity of sinus arrhythmias not due to respiration. Essentially the same changes in cardiac rhythm were observed in four young volunteers during continuous ECG recordings over a period of 9 hours in response to the repeated administration of C 50 005/A Ba in a dosage of 15 mg three times a day on two consecutive days. The differences from the corresponding placebo values were however not statistically significant.

C 50 005/A Ba is thus an orally active cardio stimulant agent with a high degree of  $\beta_1$  receptor selectivity and with only a very slight arrhythmogenic potential. It is well tolerated and could afford beneficial effects in the treatment of heart failure or as a countermeasure in therapy with  $\beta$  blockers.

### REFERENCES

- 1 Akhtar N, Mikulic E, Cohn J N and Chaudhry M H. Hemodynamic effect of dobutamine in patients with severe heart failure. *Am J Cardiol* 36:202 1975.
- 2 Beregowich J, Bianchi C, D'Angelo R, Diaz R and Rubler M. Haemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure. *Br Heart J* 37:679 1975.
- 3 Bonelli J, Magometshchag D and Hitzenträger G. A model to differentiate between  $\beta_1$  receptors mediating a specific effect on the heart rate and others mediating a positive inotropic effect. *Intern J Clin Pharmacol Biopharm* 14:231 1976.
- 4 Bühler F R, Burkart F, Lutold B E, Kung M, Warbet G and Pfisterer M. Antihypertensive beta blocking action as related to renin and age: a pharmacologic tool to identify pathogenetic mechanisms in essential hypertension. *Am J Cardiol* 36:653 1975.
- 5 Carlsson M, Dahlöf C G and Hedberg A. Differentiation of cardiac chronotropic and inotropic effects of  $\beta$  adrenoceptor agonists. Naunyn-Schmiedeberg's Arch Pharmacol (Submitted for publication).
- 6 CIBA-GEIGY Ltd. Orientation for clinical investigators C50 005/A Ba (H 80/G.) and its active L-enantiomer CGP 7760/B: a cardioselective  $\beta$  receptor stimulant. Basel 1976.
- 7 Clarke J M, Hamer J, Shelton J R, Taylor S and Vennart G R. The rhythm of the normal human heart. *Lancet* II:508 1976.
- 8 Dietz A and Kirchhoff H W. Die Variationsbreite von Herzrhythmusstörungen bei Herzgesunden. *Z Kardiol* 62:289 1973.
- 9 Dollery C T., Füllath F and Lewis G R. J. Cardiovascular effects of dobutamine. *Proc. Br Pharmacol Soc* January 1975 c 20.
- 10 Engel U R and Burckhardt D. Häufigkeit und Art von Rhythmusstörungen sowie EKG-Veränderungen bei jugendlichen Herzgesunden. *Progradien Schweiz Med Wschr* 105:1467 1975.
- 11 Farns J V, McHenry P L, Jordan J W and Morris S N. Prevalence and reproducibility of exercise induced ventricular arrhythmias during maximal exercise testing in normal men. *Am J Cardiol* 37:17 1976.
- 12 Gillespie T A, Roberts R, Ambros H D and Sobel



$\beta$  receptors due to aging is a matter for speculation. This finding is concordant with the observations by Buhler and colleagues,<sup>4</sup> who reported that the extent to which the  $\beta$  receptors could be blocked in hypertensive patients diminished with age.

Another object of the present study was to ascertain whether the cardioselective  $\beta$  adrenergic receptor stimulant effect of C 50 005/A Ba is inevitably associated with an arrhythmogenic effect, such as the catecholamines are known to produce. Several authors<sup>1,2,3</sup> maintain that dobutamine has no such effect, but their conclusions are based on observations made in patients confined to bed. There have also been reports to the contrary. Loeb and associates<sup>10</sup> and Gunnar and co workers,<sup>11</sup> for instance, noted an increase in the frequency of ventricular extrasystoles during the infusion of dobutamine in patients with heart failure. The fact that ventricular and supraventricular extrasystoles can also occur in persons free of any cardiac disorders makes it extremely difficult to assess the arrhythmogenic potential of a drug. The published incidences of extrasystoles in healthy persons vary widely, in one study Engel and Burckhardt<sup>10</sup> recorded an incidence of 31 per cent whereas Dietz and Kirchhoff<sup>8</sup> and Clarke and collaborators<sup>9</sup> quote figures up to 70 per cent and 72 per cent. McHenry and co workers<sup>7</sup> found a clear correlation between age and the occurrence of extrasystoles during maximum effort on a treadmill. In a later study the same authors<sup>11</sup> also observed that the individual reproducibility of effort induced ventricular extrasystoles in two consecutive tests was not more than 55 to 62 per cent depending on age. According to Jelinek and Lown<sup>12</sup> it was even below 50 per cent. Moreover, studies carried out by various investigators have shown that both the frequency and the type of arrhythmias occurring in clinically sound hearted persons differ greatly.<sup>7,8,10</sup> Conclusions as to the possible arrhythmogenic potential of a drug can only be reached if the ECG is recorded continuously over many hours. This was done in our study and in addition to pursuing their normal everyday activities after being treated with the substance, the subjects were also repeatedly subjected to a submaximum workload on the bicycle ergometer to increase the likelihood of arrhythmias becoming manifest by raising sympathetic tone. It was found that C 50 005/A Ba caused a slight statis-

tically nonsignificant and non dose related increase in the frequency of supraventricular and ventricular extrasystoles and an increase in the frequency and degree of marked sinus arrhythmias which at the highest tested dose level of 20 mg was just barely significant in relation to the placebo values. Marked sinus arrhythmias such as we observed in seven of our eight subjects were seen by Engel and Burckhardt<sup>10</sup> in 34 per cent of their group of young subjects. Dietz and Kirchhoff<sup>8</sup> noted changes in the P wave with an abrupt, distinct slowing of heart rate in 55 per cent of their series of 30 to 40 year old subjects. These changes seem to arise in predominantly vagotonic phases, above all in relatively young asthenic individuals. The possibility that they may be due to depression of the sinus node pacemaker has been discussed.<sup>8,9</sup> The increase in sinus arrhythmias of this type after the administration of C 50 005/A Ba likewise seems to result from transient elevations of vagal tone caused by a baroreceptor response to the increase in stroke volume or blood pressure or both.<sup>13</sup> Like all other inotropic catecholamines the substance would thus appear to have a certain though slight arrhythmogenic potential. The clinical significance of this effect can only be assessed by further careful investigation, preferably in patients with heart disease.

The occurrence of a marked depression of the ST segment in one of the elder subjects after the administration of C 50 005/A Ba can be interpreted as a manifestation of latent coronary disease. It is not surprising that the substance should provoke this effect since it augments stroke volume and heart rate, and in the absence of vasodilatation also leads to a relative increase in afterload with a corresponding rise in the myocardial oxygen requirement. It is conceivable that a preparation of this type could be employed diagnostically in a simple test of cardiac function similar to that suggested by Rivier and colleagues<sup>14</sup> based on the infusion of isoprenaline. At all events this finding underlines the need for the utmost caution in the further evaluation of the compound if it is administered to patients with coronary disease.

### Conclusions

On the basis of the available data preparation C 50 005/A Ba would appear to merit clinical trial in all acute and chronic disorders associated

# Mechanism of antihypertensive effect of thiazide diuretics

Shaukat Shah M D  
Ibrahim Khatir M D  
Edward D Freis M D  
Washington D C

The thiazide diuretics have become established as the drugs of first choice in the treatment of hypertension. Not only do they exert an independent antihypertensive effect but they also enhance the action of other antihypertensive drugs and prevent the development of resistance to various adrenergic blocking and vasodilator agents used for treating hypertensive patients.

The mechanism of the antihypertensive effect of the thiazides has not been clarified. Pharmacological textbooks<sup>1</sup> ascribe the antihypertensive action to two mechanisms as follows: (1) depletion of extracellular fluid volume (ECF) including plasma volume accounting for the initial fall of blood pressure, followed by (2) decreased peripheral vascular resistance due to a direct vasodilator action of the drug. It is generally believed that the vasodilator action contributes importantly to the long term antihypertensive effect of these drugs.<sup>2</sup> The presently accepted theory of the antihypertensive action of the thiazides therefore defines two entirely separate mechanisms: a diuretic and a vasodilator action. Furthermore, they are said to act primarily in sequence rather than together. Such a dual theory however must be regarded with suspicion because (1) it is unusual for any drug to exert its therapeutic effect via one mode of action initially and via an entirely different mechanism later on, and (2) a direct vasodilator effect of the thiazides has never been convincingly demonstrated.

In the present investigation the mode of action of the thiazides has again been investigated by recording both the short and long term effects of hydrochlorothiazide. Among the hemodynamic parameters investigated are cardiac output, plasma volume and ECF. Using these data as well as previous reports in the literature a unitary rather than the present dual theory of the mode of action of the thiazides will be presented.

## Methods

Thirteen patients with essential hypertension of mild to moderate severity who were attending the Hypertension Clinic of the Veterans Administration Hospital consented to participate in the study after being fully informed of its design and purposes. The patients either were previously untreated or were receiving thiazide diuretics without other drug treatment. Prior to the control determinations the latter patients were placed on placebos for a 2 to 3 week period. Pill counts were carried out throughout the trial as a test of compliance. One patient dropped out while another was noncompliant as judged by the pill counts. Both were dropped from the study.

The patients were studied on four occasions as follows: before treatment, 48 hours after beginning treatment with hydrochlorothiazide 50 mg twice daily to determine acute effects of the drug, and 6 weeks as well as 8 weeks after beginning treatment with hydrochlorothiazide for assessing long term effects.

During test days patients came to the laboratory in the fasting state. An 18 gauge Teflon catheter was inserted into an antecubital vein to facilitate blood sampling. Plasma volume and extracellular fluid measurements were determined in eight patients by the method of Gregersen and Stewart<sup>3</sup> adapted for use with the

From the Department of Senior Medical Investigator, Veterans Administration Hospital, and the Department of Medicine, Georgetown University, Washington, D. C.

Received for publication April 5, 1977.

Accepted for publication July 8, 1977.

Reprint requests: Edward D. Freis, M.D., Senior Medical Investigator, Veterans Administration Hospital, 50 Irving Street, N.W., Washington, D. C. 20422.

- H E Salutory effects of dobutamine on hemodynamics without exacerbation of arrhythmia or myocardial injury *Circulation* 52 (Suppl 2) 76 1975
- 13 Gunnar R M Loeb H S Klodnycky M Sinno M and Towne W Hemodynamic effects of dobutamine in man *Circulation* 48 (Suppl 4) 132 1973
  - 14 Holter N J New method for heart studies *Science* 134 1214 1961
  - 15 Jelinek M V and Lown B Exercise stress testing for exposure of cardiac arrhythmias *Progr Cardiovasc Dis* 13 497 1974
  - 16 Johnsson G Jordo L Lundborg P Ronn O Welin Fogelberg I and Wikstrand J Hemodynamic and tolerance studies in man with a new orally active selective beta 1 adrenoceptor agonist *Clin Pharmacol Ther* (Submitted for publication)
  - 17 Kattus A A and the Committee on Exercise Exercise testing and training of apparently healthy individuals A handbook for physicians New York 1972 American Heart Association
  - 18 Loeb H S Khan M Towne W Meadows W R Moffat J and Gunnar R M Comparative hemodynamic effects of dobutamine and isoproterenol in patients with cardiac failure *Clin Res* 22 286A 1974
  - 19 Loeb H S Khan M Klodnycky M L Sinno M Z Towne W D and Gunnar R M Hemodynamic effects of dobutamine in man *Circ Shock* 2 29 1975
  - 20 Lottenbach K and Scharf R Die Pressorezeptoren funktion und ihre Beziehung zu Alter und Hochdruck *Schweiz Med Wschr* 87 858 1957
  - 21 McHenry P L Fisch C Jordan J W and Corya H R Cardiac arrhythmias observed during maximal treadmill exercise testing in clinically normal men *Am J Cardiol* 29 331 1972
  - 22 Mehta J L and Cohn J N Dissociation of inotropic from chronotropic effects of isoproterenol during beta blockade with Labetalol (Sch 15719 W) *Clin Res* 24 423A 1976
  - 23 Meyer S L Curry G C Donsky M S Twieg D B Parkey R W and Willerson J T Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease *Am J Cardiol* 38 103 1976
  - 24 Rivier J L Jaeger M and Jonas N Isuprel et diagnostic électrique de l'insuffisance coronarienne *Schweiz Med Wschr* 103 348 1973
  - 25 Robinson J L Rich J M and Weissler A M Differential effects of propranolol on the chronotropic and inotropic response to isoproterenol in man *Am J Cardiol* 31 155 1973
  - 26 Weissler A M Harris W S and Schoenfeld C D Systolic time intervals in heart failure in man *Circulation* 37 149 1968
  - 27 Wirtzfeld A and Baedeker W D Rhythmusstörungen des Herzens Munich 1976 Urban & Schwarzenberg p 24

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore, all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

Table I Hemodynamic changes from control at 48 hours 6 weeks and 8 weeks after beginning treatment with hydrochlorothiazide

| Parameter  | No of cases | Control | During treatment |                |         |                |         |                |
|--|-------------|---------|------------------|----------------|---------|----------------|---------|----------------|
|  |             |         | 48 Hours         |                | 6 Weeks |                | 8 Weeks |                |
|  |             | Mean    | Mean             | P <sup>a</sup> | Mean    | P <sup>a</sup> | Mean    | P <sup>a</sup> |
| Body weight (lbs)  | 11          | 201     | 197              | < 005          | 197     | < 05           | 196     | < 01           |
| Hematocrit (%)   | 11          | 40.4    | 43.1             | < 005          | 42.6    | < 0005         | 42.7    | < 0005         |
| Plasma volume (L)  | 8           | 3.69    | 3.23             | < 005          | 3.33    | < 005          | 3.47    | NS             |
| Extracellular fluid volume (L)                           | 8           | 20.4    | 18.0             | < 005          | 16.4    | < 0005         | 15.4    | < 005          |
| Systolic blood pressure (mm Hg)                          | 11          | 153     | 135              | < 01           | 130     | < 01           | 131     | < 005          |
| Diastolic blood pressure (mm Hg)                         | 11          | 103     | 95               | < 05           | 92      | < 025          | 91      | < 01           |
| Heart rate (per min)                                     | 11          | 76      | 79               | NS             | 78      | NS             | 77      | NS             |
| Cardiac output (L/min)                                   | 11          | 6.4     | 5.4              | < 025          | 6.4     | NS             | 6.0     | NS             |
| Total peripheral resistance (Dynes cm <sup>-2</sup> sec) | 11          | 1479    | 1716             | 08             | 1356    | NS             | 1393    | NS             |

Change from control using 1 tailed test.

Table II Simultaneous determination of cardiac output by the Cardiogreen dye and CO<sub>2</sub> rebreathing methods

| Patient No | Control period            |                            |                                 |  | After 8 weeks of thiazide treatment |                            |                                |  |
|------------|---------------------------|----------------------------|---------------------------------|--|-------------------------------------|----------------------------|--------------------------------|--|
|            | Cardiac output CO (L/min) | Cardiac output Dye (L/min) | Mean arterial pressure† (mm Hg) | Total peripheral resistance (Dynes cm <sup>-2</sup> sec) | Cardiac output CO (L/min)           | Cardiac output Dye (L/min) | Mean arterial pressure (mm Hg) | Total peripheral resistance (Dynes cm <sup>-2</sup> sec) |
| 6          | 7.85                      | 6.83                       | 115                             | 1346   | 6.80                                | 8.3                        | 110                            | 1294   |
| 8          | 7.39                      | 6.37                       | 151                             | 1897   | 4.98                                | 5.83                       | 95                             | 1303   |
| 9          | 8.06                      | 6.71                       | 113                             | 1346   | 6.02                                | 6.15                       | 105                            | 1482   |
| 10         | 5.91                      | 4.90                       | 133                             | 2111   | 6.90                                | 6.45                       | 123                            | 1425   |
| 11         | 1.02                      | 7.19                       | 92                              | 1023   | 6.22                                | 6.01                       | 87                             | 1158   |
| Mean       | 7.11                      | 6.40                       | 121                             | 1557   | 6.50                                | 6.25                       | 104                            | 1352   |
| SD         | 0.11                      | 0.89                       | 22                              | 466  | 0.13                                | 0.38                       | 14                             | 150  |

Dye outputs used to calculate total peripheral resistance

†Direct intra-arterial recording of blood pressure

measured directly using a Statham strain gauge. After injecting rapidly 5 mg Cardiogreen in one ml distilled water into the central vein using a flush of 5 ml saline blood was withdrawn from the brachial artery through a Gilford densitometer using a motor driven withdrawal syringe. The resulting dye-concentration curve was recorded on a Hewlett Packard oscillographic recorder. Because of the more invasive nature of the procedure three dye curves were recorded only during the control period and again at 8 weeks following initiation of treatment. It was not considered necessary to determine the acute effects of thiazides on cardiac output with the dye technique because such early effects as were determined by the dye dilution method have

already been well defined.<sup>11</sup> The dye dilution method was used primarily to confirm the results obtained with the noninvasive CO<sub>2</sub> method on the effects of long term treatment with the thiazides.

### Results

Cardiac output blood pressure total peripheral resistance and heart rate. Cardiac output as determined by the CO<sub>2</sub> rebreathing method fell significantly ( $P < 0.05$ ) from a mean value of 6.4 L per minute during the control period to 5.4 L per minute 48 hours after beginning hydrochlorothiazide (Table I Fig 1). However 6 and 8 weeks after beginning treatment with hydrochlorothiazide cardiac output rose to or toward the

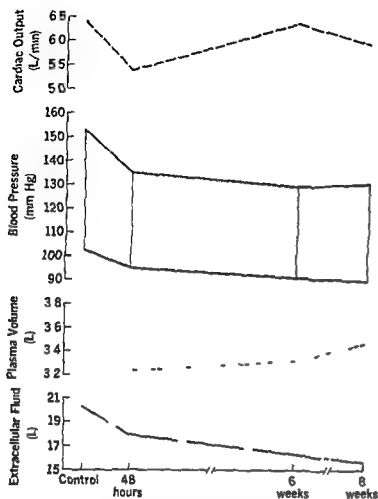


Fig 1 Mean changes in cardiac output blood pressure plasma volume and extracellular fluid volume (thiocyanate space) before as well as 48 hours 6 weeks and 8 weeks after treatment with hydrochlorothiazide

spectrophotometer. The procedures were carried out after the patients had remained continuously in the recumbent position for at least 30 minutes. After drawing control samples of blood 22.5 mg of Evans Blue dye in 5 ml of distilled water and 18 ml of 5 per cent sodium thiocyanate were injected into an antecubital vein using calibrated syringes. Blood samples were drawn from a vein in the opposite arm for plasma volume determination at 10, 15, and 20 minutes after the injection of Evans Blue dye. The concentrations at these times were plotted on semilog paper and a best fit line was extrapolated back to zero time. The latter concentration was taken as the value present after mixing and before any disappearance of the dye.

Blood samples were drawn for thiocyanate determinations at 2 hours following injection as well as 10 minutes later. Thiocyanate concentration of the second sample was required to agree within 5 per cent of the first. The average concentration of these two samples corrected for the plasma blank was used to determine the

thiocyanate space.<sup>3</sup> While this method only approximates the true extracellular fluid volume since the thiocyanate ion enters red cells and other compartments prior experience indicated that this method is reliable for measuring changes in the ECF.<sup>4</sup>

Cardiac outputs were determined by the CO rebreathing method alone in six patients and by the CO<sub>2</sub> rebreathing method and the dye dilution methods in five patients. Cardiac output was determined by the CO<sub>2</sub> rebreathing method before the administration of hydrochlorothiazide and 48 hours 6 weeks and 8 weeks after initiating treatment with the drug. After resting in the supine position for at least ten minutes the blood pressure was recorded by the same observer throughout, using the standard auscultatory method. The fifth phase of the Korotkoff sounds were used as the indication of diastolic blood pressure. The blood pressure was recorded before and after each determination of cardiac output and the results were averaged. The initial determinations of blood pressure and cardiac output were discarded in order to accustom the patient to the procedure prior to the collection of data. Cardiac output also was determined by the dye method in five of the patients before beginning treatment with hydrochlorothiazide and 8 weeks after beginning treatment. The significance of differences after as compared to before treatment was determined using Student's *t* test.

The technique of Franciosa and associates<sup>5</sup> was used for estimating cardiac output by the CO<sub>2</sub> rebreathing method. Their technique was modified slightly with respect to the point at which CO<sub>2</sub> is measured in the expired air. Rather than using forced expiration which in our hands frequently lead to an overestimate of alveolar CO<sub>2</sub>, we recorded the CO<sub>2</sub> concentration in expired air during normal or deep respiration at a point where the expired volume approximated 400 ml. The CO<sub>2</sub> concentration and the respiratory volume were recorded continuously and simultaneously. The 400 ml point was chosen because it well exceeded the dead space volume of 150 to 250 ml but was not so large as to reflect the CO<sub>2</sub> concentration in underventilated alveoli such as we had experienced using forced expiration.

For the dye dilution method a polyethylene catheter was inserted into an antecubital vein and was threaded into a central vein. A Teflon catheter was then inserted via a needle into the brachial artery. Mean arterial blood pressure was

reflex increase in heart rate and cardiac output similar to that seen with other vasodilator drugs such as hydralazine or amyl nitrite. Acute administration of the thiazides however is associated with the opposite hemodynamic effects that is with an increase in total peripheral resistance and a fall in cardiac output.<sup>11</sup> Also the initial observation<sup>14</sup> that hypotension preceded the diuresis has not been confirmed as three other investigations concluded that the fall in blood pressure occurred only after an effective diuresis.<sup>15</sup> Furthermore a direct vasodilator effect of the thiazide diuretics has not been convincingly demonstrated.

The vasodilator theory of the action of the thiazides has been further questioned by the observation that other diuretics such as parenteral mercurials and ethacrynic acid<sup>16</sup> also exhibit an antihypertensive effect. These drugs have in common volume depleting effects rather than vasodilator properties. Also the reduction of blood pressure occurring in patients receiving the low sodium rice diet is associated with a significant reduction in ECF.<sup>17</sup> All of the above antihypertensive procedures decrease ECF suggesting that it is the latter which is causally implicated in the reduction of blood pressure in both the acute and chronic responses.

Volume depletion following acute administration of the thiazides has been documented by many investigators.<sup>18-21</sup> Patients undergoing continuous treatment with thiazides lose about 2 L of ECF and about 300 to 400 ml of plasma volume during the first 72 hours of treatment. After this time there is no additional volume depletion. However the reduction in ECF which occurs during the first 72 hours is maintained. Patients receiving diets severely restricted in sodium show quantitatively similar reductions averaging 10 per cent of the ECF and 15 per cent of the plasma volume.<sup>22</sup>

The importance of reduced volume is again indicated by observations that the antihypertensive effects of combined treatment with thiazide diuretics and adrenergic blocking agents can be reversed in many patients by re-expanding the plasma volume with salt free dextran.<sup>23-25</sup> However in patients treated with thiazides without adrenergic blocking agents dextran will only occasionally but not usually restore the hypertension. Nevertheless oral ingestion of 20 to 30 Gm salt which is sufficient to re-expand

total ECF despite the administration of thiazides does restore the hypertension even during long term treatment.<sup>26</sup> This suggests that re-expansion of total ECF rather than plasma volume alone is required to overcome completely the antihypertensive effects of the thiazides.

Three possible mechanisms can be postulated to explain how thiazide induced reduction of ECF lowers blood pressure. Firstly volume depletion may blunt environmental pressor stimuli while at the same time enhancing depressor influences. For example patients receiving ganglion blocking agents often exhibit marked hypotensive responses with only small reduction of blood volume.<sup>27</sup> It has further been observed that following either thiazide or mercurial induced diuresis the depressor responses to infused trimethaphan are increased.<sup>28</sup> Also expansion of ECF in rats results in an enhanced pressor response to angiotensin whereas ECF depletion has the opposite effect.<sup>29</sup> Volume depletion therefore seems to dampen pressor reactions and increase depressor responses the combined effects of which could result in a reduction of average blood pressure. While this theory is attractive it does not explain the rise in cardiac output toward control values and fall in total peripheral resistance which occurs with long term treatment.

The second possible mechanism by which volume depletion may lower blood pressure is via the baroreceptor reflexes. It has been noted clinically that elderly patients often exhibit an enhanced hypotensive response to the thiazide diuretics requiring reduction of dosage often to quite small amounts. On the other hand young normal adults do not show an antihypertensive effect with the thiazide diuretics although their heart rates increase significantly consistent with an active baroreceptor response to the lower blood pressure associated with the volume depletion.<sup>30</sup> Elderly normal subjects however do show a fall of blood pressure with the thiazide diuretics.<sup>30</sup>

Baroreceptor reflex responses depend upon the compliance of the aorta and carotid artery. These vessels become less distensible as a result of structural changes induced by aging or by hypertension. Homeostatic circulatory adjustment to pressor stimuli are poorly moderated in long standing chronic hypertension.<sup>31</sup> While the evidence is incomplete it is consistent with the

pretreatment values and was then insignificantly different from the pretreatment control level

Cardiac output determined by the dye method in five patients agreed reasonably well with the cardiac output determined by the  $\text{CO}_2$  rebreathing method (Table II). The correlation coefficient comparing both methods was  $r = 0.84$  ( $P < 0.05$ ) during the control period and  $r = 0.97$  ( $P < 0.05$ ) after 8 weeks of treatment. After 8 weeks the mean change in cardiac output from pretreatment control was  $-0.2$  L and  $-0.6$  L for the dye and  $\text{CO}_2$  rebreathing methods, respectively. Neither change was significant.

By contrast to the initial fall and later return of cardiac output, the blood pressure fell early and remained reduced (Table I, Fig. 1). The average control blood pressure of 153/103 fell to 135/95 mm Hg after 48 hours ( $P < 0.05$ ). After 6 and 8 weeks of treatment the blood pressure was even lower averaging 130/92 and 131/91 mm Hg at 6 and 8 weeks respectively ( $P < 0.025$ ).

Total peripheral resistance increased initially from a mean of 1479 dynes  $\text{cm}^{-5}$  sec in the control period to 1716 dynes  $\text{cm}^{-5}$  sec 48 hours after beginning hydrochlorothiazide. The change was of borderline significance ( $P = 0.09$ ). After 6 and 8 weeks, total peripheral resistance decreased slightly but not significantly below the control level; the mean values being 1356 and 1393 dynes  $\text{cm}^{-5}$  per second respectively at the 6 and 8 week post treatment periods.

Heart rate did not change significantly throughout the treatment period. The mean value for heart rate rose insignificantly from 76 per minute in the pretreatment period to 79 per minute at 48 hours after beginning treatment. The mean values for heart rate at 6 and 8 weeks after beginning treatment remained within the range of these values.

Extracellular fluid volume, plasma volume, hematocrit and body weight. ECF measured in eight patients by the thiocyanate method fell significantly and remained reduced throughout the period of observation (Table I). From a mean control value of 20.4 L, the ECF decreased 12 per cent to 18.0 L at 48 hours after beginning hydrochlorothiazide. The reductions in ECF were even greater at 6 and 8 weeks, averaging 20 and 24 per cent, respectively, below the control mean.

Plasma volume decreased from a mean of 3.69 L in the control period to 3.23 L 48 hours after beginning treatment with hydrochlorothiazide.

The decrease averaged 13 per cent and was highly significant ( $P < 0.005$ ). Plasma volume remained reduced at 6 and 8 weeks after treatment with hydrochlorothiazides, although the change attained statistical significance only at the 6 weeks interval.

Reflecting the decrease in plasma volume the hematocrit rose and remained significantly above the control mean throughout the 8 week period of treatment. The mean value in the control period was 40.4 and this rose to 43.1 after 48 hours of treatment, an increase of 7 per cent. The mean values at 6 and 8 weeks of treatment were essentially the same as at 48 hours (Table I).

Body weights decreased at 48 hours after treatment and remained significantly below the control for the remainder of the period of observation. The average loss of weight was 4 pounds or 1.8 kilograms at 48 hours, increasing to 5 and 6 pounds (2.3 and 2.7 kilograms) respectively, at 6 and 8 weeks after beginning treatment.

## Discussion

Three principal hypotheses have been advanced to explain the antihypertensive effects of the thiazide diuretics. The first two hypotheses are concerned with sodium depletion of which one ascribes the fall in blood pressure to a reduction in total ECF and the other to a loss of sodium from the arterial walls. The latter hypothesis probably can be discarded because studies from three independent sources found no evidence that thiazides affect the sodium content of either large or small arteries in rats.<sup>11</sup> The third and most popular hypothesis is that the hypotensive effect at least during chronic treatment, is due to a direct vasodilator effect of these drugs.<sup>12</sup>

Hollander, Chobanian, and Wilkins<sup>13</sup> found no reduction in extracellular fluid volume after one to six months of treatment with chlorothiazide. On the basis of this and other data, they concluded that the antihypertensive effect was not due solely to sodium depletion. Their conclusion gained support from the observation that the chemically related compound diazoxide<sup>14</sup> is a vasodilator antihypertensive compound which produces sodium retention rather than diuresis.<sup>15</sup> According to Rowe and colleagues,<sup>16</sup> acute administration of diazoxide is associated with a considerable decrease in total peripheral resistance in hypertensive patients and with a

reflex increase in heart rate and cardiac output similar to that seen with other vasodilator drugs such as hydralazine or amyl nitrite. Acute administration of the thiazides however is associated with the opposite hemodynamic effects that is with an increase in total peripheral resistance and a fall in cardiac output.<sup>1,4</sup> Also the initial observation that hypotension preceded the diuresis has not been confirmed as three other investigations concluded that the fall in blood pressure occurred only after an effective diuresis.<sup>5,6</sup> Furthermore a direct vasodilator effect of the thiazide diuretics has not been convincingly demonstrated.

The vasodilator theory of the action of the thiazides has been further questioned by the observation that other diuretics such as parenteral mercurials<sup>7</sup> and ethacrynic acid<sup>8</sup> also exhibit an antihypertensive effect. These drugs have in common volume depleting effects rather than vasodilator properties. Also the reduction of blood pressure occurring in patients receiving the low sodium rice diet is associated with a significant reduction in FCF.<sup>9,10</sup> All of the above antihypertensive procedures decrease ECF suggesting that it is the latter which is causally implicated in the reduction of blood pressure in both the acute and chronic responses.

Volume depletion following acute administration of the thiazides has been documented by many investigators.<sup>11</sup> Patients undergoing continuous treatment with thiazides lose about 2 L of ECF and about 300 to 400 ml of plasma volume during the first 72 hours of treatment. After this time there is no additional volume depletion. However the reduction in ECF which occurs during the first 72 hours is maintained. Patients receiving diets severely restricted in sodium show quantitatively similar reductions averaging 10 per cent of the ECF and 15 per cent of the plasma volume.<sup>12</sup>

The importance of reduced volume is again indicated by observations that the antihypertensive effects of combined treatment with thiazide diuretics and adrenergic blocking agents can be reversed in many patients by reexpanding the plasma volume with salt free dextran.<sup>13,14</sup> However in patients treated with thiazides without adrenergic blocking agents dextran will only occasionally but not usually restore the hypertension. Nevertheless oral ingestion of 20 to 30 Gm salt which is sufficient to reexpand

total ECF despite the administration of thiazides does restore the hypertension even during long term treatment.<sup>15</sup> This suggests that reexpansion of total FCF rather than plasma volume alone is required to overcome completely the antihypertensive effects of the thiazides.

Three possible mechanisms can be postulated to explain how thiazide induced reduction of ECF lowers blood pressure. Firstly volume depletion may blunt environmental pressor stimuli while at the same time enhancing depressor influences. For example patients receiving ganglion blocking agents often exhibit marked hypotensive responses with only small reduction of blood volume.<sup>16</sup> It has further been observed that following either thiazide or mercurial induced diuresis the depressor responses to infused trimethaphan are increased.<sup>17</sup> Also expansion of ECF in rats results in an enhanced pressor response to angiotensin whereas ECF depletion has the opposite effect.<sup>18</sup> Volume depletion therefore seems to dampen pressor reactions and increase depressor responses the combined effects of which could result in a reduction of average blood pressure. While this theory is attractive it does not explain the rise in cardiac output toward control values and fall in total peripheral resistance which occurs with long term treatment.

The second possible mechanism by which volume depletion may lower blood pressure is via the baroreceptor reflexes. It has been noted clinically that elderly patients often exhibit an enhanced hypotensive response to the thiazide diuretics requiring reduction of dosage often to quite small amounts. On the other hand young normal adults do not show an antihypertensive effect with the thiazide diuretics although their heart rates increase significantly consistent with an active baroreceptor response to the lower blood pressure associated with the volume depletion.<sup>19</sup> Elderly normal subjects however do show a fall of blood pressure with the thiazide diuretics.<sup>20</sup>

Baroreceptor reflex responses depend upon the compliance of the aorta and carotid artery. These vessels become less distensible as a result of structural changes induced by aging or by hypertension. Homeostatic circulatory adjustment to pressor stimuli are poorly moderated in long standing chronic hypertension.<sup>21</sup> While the evidence is incomplete it is consistent with the



concept that the antihypertensive effect of the thiazide diuretics, at least in patients with noncompliant arteries, could be due in part to an inadequate baroreceptor compensation for the volume depletion and reduced cardiac output.

The third, and we believe most likely mechanism, for explaining the hemodynamic changes seen with the thiazide diuretics involves feedback autoregulatory responses to a prolonged reduction in cardiac output as originally suggested by Tobian.<sup>1-3</sup> Such feedback autoregulatory systems have been postulated to explain the rise of blood pressure which occurs in certain types of experimental hypertension. In experimental renovascular hypertension<sup>4</sup> or in the hypertension caused by reduction in renal mass plus salt loading<sup>5</sup> or in the hypertension induced by excess licorice ingestion in man<sup>6</sup> the following sequence of events was observed during the development of the hypertension: (1) salt and water retention, leading to (2) expansion of the ECF and plasma volume resulting in (3) increased venous pressure and venous return to the heart followed by (4) increased cardiac output, (5) rise in blood pressure leading to (6) increase in urine volume preventing further rise in ECF followed by (7) gradual elevation of total peripheral vascular resistance occurring over a period of weeks. It was postulated that the rise in total peripheral resistance was due to autoregulation in response to the elevated peripheral blood flows which were in excess of local metabolic needs because of the increased cardiac output. At the same time, there was (8) reduction of the elevated cardiac output toward normal because of the elevated afterload resulting from the increase in total peripheral resistance. Thus the hypertension which was initiated by an expansion of ECF and resulting increase in cardiac output evolved after approximately one month into a hypertension characterized by an elevated total peripheral resistance and normal cardiac output.

Tobian<sup>1-3</sup> has postulated that thiazides and related diuretics induce reverse autoregulation which leads to a decrease in total peripheral resistance. Thus reduction in ECF caused by thiazides produce initially a fall in central venous pressure, venous return and cardiac output. At first, this is associated with an increased total peripheral resistance. However with continued treatment and maintained reduction in cardiac output and total blood flow, autoregulation

occurs gradually over a period of weeks leading to a decline in total peripheral resistance. Finally, we suggest that the resulting fall in afterload permits a rise in cardiac output toward normal. This sequence of hemodynamic events is the same as that actually observed during the early and late phases of continuous treatment with the thiazides and they all follow from a single hemodynamic effect of the thiazides which is a sustained reduction in ECF. No direct vasodilator action of the thiazides need to be postulated as the early fall and later return of cardiac output to normal and the early rise and later fall in total peripheral resistance can both be explained by the reduction in ECF alone.

Most pharmacological textbooks differentiate between the short term and long term effects of thiazides.<sup>1-3</sup> According to these texts the short term antihypertensive effect is due primarily to volume depletion while the long term effect is ascribed to a vasodilator action of the thiazides. The principal evidence for such a dual mechanism of action is the report of Conway and Lauwers,<sup>37</sup> which indicates that plasma volume and ECF fall initially but then return to essentially control values after one month of continuous treatment with chlorothiazide. These investigators concluded that decreased ECF could not have an influence on the long term antihypertensive effect of the thiazides.

Other investigators, however, have not corroborated the observations of Conway and Lauwers. Wilson and Freis<sup>4</sup> found a significant reduction of ECF after six months of continuous treatment with chlorothiazide. Plasma volume also was reduced at six months although not significantly. However, at 12 months plasma volume was significantly lower than control. More recently, other investigators also found a continued reduction of plasma volume and ECF during long term treatment with thiazides.<sup>38,39</sup> Furthermore following withdrawal of long term treatment there was a prompt and significant rise of plasma volume, ECF and blood pressure providing further evidence that the thiazides continue to maintain their volume reducing effect during chronic administration.<sup>40</sup>

Conway and Lauwers<sup>37</sup> also observed that while cardiac output falls initially after administration of thiazide it returns to normal after one month. The latter observation has been confirmed in the present study and by Lund-Johan

sen<sup>44</sup> During the first few days of treatment cardiac output is reduced and total peripheral resistance is increased<sup>44</sup> However after a month or more of treatment cardiac output rises to or toward control values while total peripheral resistance falls These changes can be explained by reverse autoregulation without invoking a separate vasodilator effect of the thiazide diuretics

Autoregulation may not be limited to the thiazides alone Other antihypertensive agents also induce differing hemodynamic effects during acute and chronic administration Guanethidine an adrenergic blocking agent causes an initial fall in cardiac output but with long term treatment cardiac output rises gradually back toward normal<sup>45</sup> Hydralazine a vasodilator agent initially increases cardiac output but the latter returns toward normal during chronic treatment<sup>46</sup> These observations suggest that autoregulatory responses which return the cardiac output toward normal often occur during long term administration of antihypertensive agents

# Summary

Hemodynamic studies were carried out before and during 8 weeks of treatment with hydrochlorothiazide 50 mg twice daily in 11 hypertensive patients Forty eight hours after beginning treatment there was a significant reduction in blood pressure cardiac output plasma volume and extracellular fluid volume (thiocyanate space) while total peripheral resistance increased After 6 and 8 weeks of treatment the blood pressure and the plasma and extracellular volumes remained reduced However total peripheral resistance fell while cardiac output rose to control levels These results were consistent with the reverse autoregulation theory of the action of the thiazides as proposed by Tobian The present findings as well as other clinical and experimental evidence discussed below makes it appear unlikely that the thiazides have an important direct vasodilator effect

# REFERENCES

1. Aviado D M Pharmacologic principles of medical practice ed 8 Baltimore 1972, The Williams & Wilkins Company p 111.
2. Nickerson M and Ruedy J Antihypertensive agents and the drug therapy of hypertension in The pharmacological basis of therapeutics, edited by Goodman L S and Gilman A New York, 1975 McMillan Publishing Co Inc, p 12.

3. Gregersen M I and Stewart J D Simultaneous determination of plasma volume with Tl<sup>201</sup> and available fluid volume with sodium thiocyanate Am J Physiol 125 142 1939
4. Wilson I M and Freis E D Relationship between plasma and extracellular fluid volume depletion and the antihypertensive effect of chlorothiazide Circulation 20 1078 1959
5. Franciosa J Ragan D O and Rubenstein S Validation of CO rebreathing method for measuring cardiac output in patients with hypertension or heart failure J Lab Clin Med 88 672, 1976
6. Croley A P Jr Castillo C Freeman D J White D H Jr and Rowe H G The acute effects of carbonic anhydrase inhibition on systemic hemodynamics J Clin Invest 37 887 1958
7. Dustan H P Cumming G R and Corcoran A C A mechanism of chlorothiazide-enhanced effectiveness of antihypertension ganglioplegic drugs Circulation 19 360 1959
8. Frolich E D Schnaper H W Wilson I M and Freis E D Hemodynamic alterations in hypertensive patients due to chlorothiazide N Engl J Med 262 1261 1960
9. Tobian L Janacek J Foker J and Ferreira H Effect of chlorothiazide on renal juxtaglomerular cells and tissue electrolytes, Am J Physiol 202 905 1962
10. Daniel E E On the mechanism of the antihypertensive action of hydrochlorothiazide in rats Circ Res 11 941 1967
11. Weller J M and Haight A S Effect of chlorothiazide on blood pressure and electrolytes of normotensive and hypertensive rats Proc Soc Exp Biol Med 112 870 1963
12. Hollander W, Chobanian A V, and Wilkins R W Studies on the antihypertensive action of chlorothiazide Clin Res 6 21 1958
13. Rubin A A Roth F E Taylor R III and Rosenkild H Pharmacology of diazoxide an antihypertensive nondiuretic benzothiadiazine J Pharmacol Exp Ther 136 244 1962
14. Bartorelli C Gargano N Leonetti G and Zanchetti A Hypotensive and renal effects of diazoxide a sodium retaining benzothiadiazine compound Circulation 27 895 1963
15. Rowe G G Leicht T R, Boake W C Kyle J C and Crompton C W The systemic and coronary hemodynamic effects of diazoxide AM HEART J 111 636 1963
16. Freis E D The effects of salt and extracellular fluid depletion on vascular responsiveness with particular reference to chlorothiazide in Hypertension Proceedings of the Council on High Blood Pressure Research November 1958 edited by Skelton F R New York 1959 American Heart Association p 6
17. Dollery C T, Harrington M and Kaufmann G The mode of action of chlorothiazide in hypertension with special reference to potentiation of ganglion blocking agents Lancet 1 1215 1959
18. Macleod C and Dustan H P Sequential changes evoked by chlorothiazide in hypertensive patients Arch Intern Med 106 316 1960
19. Conway J and Leonetti G Hypotensive effect of ethacrynic acid Circulation 31 661 1965
20. Murphy R J F The effect of rice diet on plasma volume and extracellular fluid space in hypertensive subjects J Clin Invest 29 912 1950
21. Warkum D M Fraeb H F Hatch F T and Gutman A B Effects of diet in essential hypertension II Results with unmodified Kemper rice diet in fifty hospitalized patients AM J Med 9 441 1950

concept that the antihypertensive effect of the thiazide diuretics, at least in patients with noncompliant arteries, could be due in part to an inadequate baroreceptor compensation for the volume depletion and reduced cardiac output.

The third and we believe most likely mechanism, for explaining the hemodynamic changes seen with the thiazide diuretics involves feedback autoregulatory responses to a prolonged reduction in cardiac output as originally suggested by Tobian.<sup>22-23</sup> Such feedback autoregulatory systems have been postulated to explain the rise of blood pressure which occurs in certain types of experimental hypertension. In experimental renovascular hypertension<sup>24</sup> or in the hypertension caused by reduction in renal mass plus salt loading,<sup>25</sup> or in the hypertension induced by excess licorice ingestion in man<sup>26</sup> the following sequence of events was observed during the development of the hypertension: (1) salt and water retention, leading to (2) expansion of the ECF and plasma volume resulting in (3) increased venous pressure and venous return to the heart, followed by (4) increased cardiac output (5) rise in blood pressure leading to (6) increase in urine volume preventing further rise in ECF followed by (7) gradual elevation of total peripheral vascular resistance occurring over a period of weeks. It was postulated that the rise in total peripheral resistance was due to autoregulation in response to the elevated peripheral blood flows which were in excess of local metabolic needs because of the increased cardiac output. At the same time, there was (8) reduction of the elevated cardiac output toward normal because of the elevated afterload resulting from the increase in total peripheral resistance. Thus the hypertension which was initiated by an expansion of ECF and resulting increase in cardiac output evolved after approximately one month into a hypertension characterized by an elevated total peripheral resistance and normal cardiac output.

Tobian<sup>22-23</sup> has postulated that thiazides and related diuretics induce reverse autoregulation which leads to a decrease in total peripheral resistance. Thus reduction in ECF caused by thiazides produce initially a fall in central venous pressure, venous return, and cardiac output. At first, this is associated with an increased total peripheral resistance. However, with continued treatment and maintained reduction in cardiac output and total blood flow, autoregulation

occurs gradually over a period of weeks leading to a decline in total peripheral resistance. Finally we suggest that the resulting fall in afterload permits a rise in cardiac output toward normal. This sequence of hemodynamic events is the same as that actually observed during the early and late phases of continuous treatment with the thiazides and they all follow from a single hemodynamic effect of the thiazides which is a sustained reduction in ECF. No direct vasodilator action of the thiazides need to be postulated as the early fall and later return of cardiac output to normal and the early rise and later fall in total peripheral resistance can both be explained by the reduction in ECF alone.

Most pharmacological textbooks differentiate between the short term and long term effects of thiazides.<sup>1-2</sup> According to these texts the short term antihypertensive effect is due primarily to volume depletion while the long term effect is ascribed to a vasodilator action of the thiazides. The principal evidence for such a dual mechanism of action is the report of Conway and Lauwers<sup>27</sup> which indicates that plasma volume and ECF fall initially but then return to essentially control values after one month of continuous treatment with chlorothiazide. These investigators concluded that decreased ECF could not have an influence on the long term antihypertensive effect of the thiazides.

Other investigators however have not corroborated the observations of Conway and Lauwers. Wilson and Freis<sup>4</sup> found a significant reduction of ECF after six months of continuous treatment with chlorothiazide. Plasma volume also was reduced at six months although not significantly. However, at 12 months plasma volume was significantly lower than control. More recently, other investigators also found a continued reduction of plasma volume and ECF during long term treatment with thiazides.<sup>28-30</sup> Furthermore following withdrawal of long term treatment there was a prompt and significant rise of plasma volume, ECF and blood pressure providing further evidence that the thiazides continue to maintain their volume reducing effect during chronic administration.<sup>4-30</sup>

Conway and Lauwers<sup>27</sup> also observed that while cardiac output falls initially after administration of thiazide it returns to normal after one month. The latter observation has been confirmed in the present study and by Lund-Johan

# Changes in components of kinin system and hemodynamics in acute myocardial infarction

Kenchi Hashimoto M D  
Hiromu Hamamoto M D  
Yuichiro Honda M D  
Masaru Hirose M D  
Soichi Furukawa M D  
Enchi Kimura M D

Tokyo Japan

The mortality rate following acute myocardial infarction has been recently reduced but remains high in patients who develop cardiogenic shock. Since the incidence of pump failure appears to be related to infarct size,<sup>1,2</sup> recent investigations have emphasized reduction of infarction by administration of various pharmacologic or mechanical interventions. However, the significance of the role of metabolic and neurohumoral factors in acute ischemic states and in the development of cardiogenic shock remains to be elucidated.

Because of its potent pain producing and hypotensive actions,<sup>3</sup> kinin has been proposed as one of the factors contributing to chest pain and development of shock in patients with angina pectoris or acute myocardial infarction.<sup>4,5</sup> These hypotheses were largely based on measurements of kininogen, the inactive precursor of kinin, yet validation of the kinin mechanisms during myocardial ischemia requires determination of sequential alterations in kinin itself along with simultaneous hemodynamic and metabolic measurements.

In our previous studies in dogs with coronary occlusion, we observed a marked increase in coronary

sinus blood kinin levels accompanied by a significant decrease in myocardial contractility.<sup>6</sup> This might indicate that the kinin release secondary to acute myocardial ischemia could be a factor in the development of cardiogenic shock. The purpose of the present study was to investigate alterations in kinin and hemodynamics in two subsets of patients with acute myocardial infarction. Subset A consisted of patients who survived more than 1 month and subset B consisted of patients who died of pump failure within 3 days of acute myocardial infarction.

## Materials and methods

The study included 23 patients who had been hospitalized in our clinic with acute myocardial infarction. Of these, 16 survived more than 1 month's observation period. The remaining seven patients died of shock or congestive heart failure within 3 days after onset of the infarction. Sites of infarction in the 16 survivors were anteroapical in nine, anterolateral in two, anteroposterior in one, posterior in three, and lateral infarction in one case. Except for occasional premature ventricular contractions, no major complications were observed in these patients. Of the seven non-surviving patients, four died of cardiogenic shock (three anteroapical and one lateral infarction) and three of congestive heart failure (one anterolateral and two posterior infarction). Sequential blood samples were taken from the cubital vein 1, 2, 3, 4, 5, 6, 7, 10, 15, 20, 25, and 30 days after the heart attack in the survivors and up to the time of death in the non-survivors. Plasma kininogen

From the First Department of Internal Medicine, Nippon Medical School.

This study was funded by a grant for Scientific Research from the Japanese Ministry of Education in 1973.

Received for publication May 25, 1977.

Accepted for publication July 5, 1977.

Reprint requests: Dr. Kenchi Hashimoto, First Department of Internal Medicine, Nippon Medical School, 115 Sendagaya Bunkyo-ku Tokyo, Japan 113.

- 22 Tapia F A, Dustan H P, Schneckloth H A, Corcoran A C and Page I H. Enhanced effectiveness of ganglion blocking agents in hypertensive patients during administration of a saluretic agent (chlorothiazide). *Lancet* 2:831 1957
- 23 Freis E D, Wanko A, Wilson I M and Parrish A E. Chlorothiazide in hypertensive and normotensive patients. *Ann N Y Acad Sci* 71:450 1958
- 24 Winer H M. The antihypertensive actions of benzothiazidines. *Circulation* 23:211 1961
- 25 McQueen E G and Morrison R H. The hypotensive action of diuretic agents. *Lancet* 1:1209 1960
- 26 Ronnov-Jessen V. Variations in blood volume during treatment of hypertension with ganglion blocking agents and thiazide perparation. *Acta Med Scand* 170:363 1961
- 27 Freis E D, Finnerty F A Jr, Schnaper H W, Stanton J R, Rath C S, Johnson R L and Wilkins R W. The collapse produced by venous congestion of the extremities or by venesection following certain hypotensive agents. *J Clin Invest* 30:453 1951
- 28 Wanko A and Freis E D. Altered vascular responses following chlorothiazide or mercurial diuresis in normotensive subjects. *Circulation* 18:792 1958
- 29 Reid W D and Laragh J H. Sodium and potassium intake, blood pressure and pressor response to angiotensin. *Proc Soc Exp Biol Med* 120:26 1965
- 30 Hoobler S. Antihypertensive effects of diuretics in Antihypertensive therapy principles and practice edited by Gross F. Heidelberg 1966. Springer Verlag p. 256
- 31 Finnerty F A Jr, Tuckman J and Hajar G. Change in heart rate during levaterenol infusion: an index of arterial elasticity. *Circ Res* 7:585 1959
- 32 Tobian L. How sodium and the kidney relate to the hypertensive arteriole. *Fed Proc* 33:138 1974
- 33 Tobian L. Hypertension and the kidney. *Arch Intern Med* 133:959 1974
- 34 Ledingham J M. Distribution of water, sodium and potassium in heart and skeletal muscle in experimental renal hypertension in rats. *Clin Sci* 12:337 1953
- 35 Guyton A C, Coleman T G, Cowley A W, Manning R D Jr, Norman H A and Ferguson J D. A systems analysis approach to understanding long range arterial blood pressure control and hypertension. *Circ Res* 35:169 1974
- 36 Borst J G G and De Borst G A. Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1:677 1963
- 37 Conway J and Lauwers P. Hemodynamic and hypotensive effects of long term therapy with chlorothiazide. *Circulation* 21:21 1960
- 38 Tarazi R C, Dustan H P and Frohlich E D. Long term thiazide therapy in essential hypertension. *Circulation* 41:709 1970
- 39 Leth A. Changes in plasma and extracellular fluid volumes in patients with essential hypertension during long term treatment with hydrochlorothiazide. *Circulation* 42:479 1970
- 40 Lund-Johansen P. Hemodynamic changes in long term diuretic therapy of essential hypertension. *Acta Med Scand* 187:590 1970
- 41 Villarreal H, Exaire J E, Rubio V and Davila H. Effect of guanethidine and bretylium tosylate on systemic and renal hemodynamics in essential hypertension. *Am J Cardiol* 14:633 1964
- 42 Reubi F C, Gossweiler N, Butikofer E and Blumberg A. Quelques aspects du reajustement circulatoire au cours du traitement antihypertensif de longue durée. In: International Club on Arterial Hypertension. Premiere Reunion July 5-7 1965, edited by Millez P, Tcherdakov P. Paris 1966. L'Expansion Scientifique Francaise p. 419

# Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P O Box 765, Schenectady, N Y 12301. 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works, or for resale.

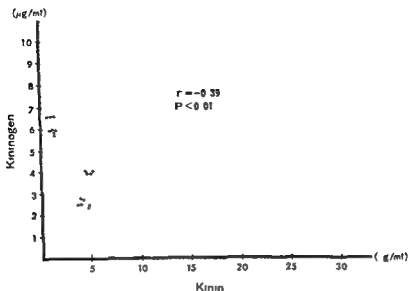


Fig 3 Relationship between kininogen and kinin levels in the same blood samples obtained from the cubital vein in surviving patients (N = 143)

the onset of infarction. Three out of the nine cases observed more than 15 days returned to normal but kinin levels remained elevated in six throughout 30 days postinfarction.

**Relationship between kininogen and kinin** The relationship between kininogen and kinin measurements was plotted in Fig 3 and a weak though significant correlation was obtained ( $r = -0.39$ ,  $p < 0.01$ ). This might indicate that kinin was activated in blood from kininogen through the action of kininogenases.

**Correlation between blood pressure, kininogen and kinin** Fig 4 illustrates changes in blood pressure, kininogen and kinin in the 16 surviving patients. The preinfarction blood pressure obtained in the outpatient clinic served as baseline control and subsequent alterations are expressed as per cent change. The blood pressure decreased on the first day of infarction by 20 per cent and dropped further to a maximum change of 28 per cent on the second day. Subsequently blood pressure recovered slightly but remained below control throughout the 30 day observation period. The correlations between lowering of blood pressure and those of kininogen and kinin levels within the first 10 days of infarction were weak but significant ( $r = -0.46$ ,  $p < 0.05$  for kininogen and  $r = 0.30$ ,  $p < 0.05$  for kinin). Thus some causal relationship might exist between the lowering of blood pressure and increased levels of

kinin substances during the early stage of acute myocardial infarction.

**Cardiac output, total peripheral resistance and circulation time** As shown by the solid columns in each panel of Fig 5, normal baseline ranges for cardiac output, total peripheral resistance and circulation time were  $4.4 \pm 0.5$  L/minute,  $1746 \pm 169$  dyne sec/cm and  $10.6 \pm 0.4$  sec, respectively. Cardiac output dropped on the first day of acute myocardial infarction (by 36 per cent) and tended to recover during the subsequent 5 days. Total peripheral resistance was elevated on the first day by 65 per cent then tended to decrease, reaching a minimal value on the fourth day from the infarction. After the seventh day, total peripheral resistance was almost back to the normal level. Circulation time increased on the first day (by 39 per cent) and reached a maximum on the second day ( $14.7 \pm 1.3$  sec). Thereafter it tended to gradually recover.

**Correlation between kinin system substances and hemodynamics** Table I summarizes the correlations between kininogen and kinin changes on the one hand and alterations in hemodynamics including blood pressure, cardiac output, total peripheral resistance and circulation time on the other. Significant negative correlations were noted between kininogen and lowering of blood pressure ( $r = -0.46$ ,  $p < 0.05$ ) as well as

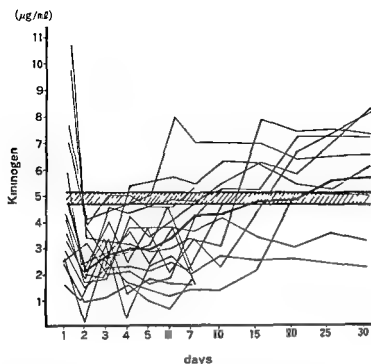


Fig 1 Changes in kininogen levels in cubital vein blood in 16 surviving patients. Mean values are shown by a thick line and individual patients are represented by thin lines. A cross hatched zone indicates normal range (mean  $\pm$  SEM).

and kinin were extracted from the blood samples according to the methods of Brocklehurst and Zeitlin<sup>10</sup> and Abe and associates,<sup>11</sup> respectively, and bioassayed using the perfused guinea pig ileum. Five healthy subjects were also used to determine control levels of the kinin system substances over a period of 7 days.

Simultaneous with blood sampling, blood pressure and heart rate were measured and cardiac output as well as circulation time (forearm to ear) was obtained by means of the dye dilution technique (Waters instruments Inc. Model PR 52). Total peripheral vascular resistance was calculated. Data were expressed as mean  $\pm$  standard error of the mean (SEM) and statistical analysis of the data was performed by the Student *t* test.

## Results

### 1. Surviving patients (16 cases)

**Kininogen.** Fig 1 illustrates changes in kininogen levels in cubital vein blood samples during the postinfarction observation period. The mean values are shown by a thick line whereas individual patients are represented by thin lines. For comparison, the baseline value of  $5.3 \pm 0.3$   $\mu\text{g/ml}$ , established in five normal subjects, is also indicated by a cross hatched zone. It is seen that

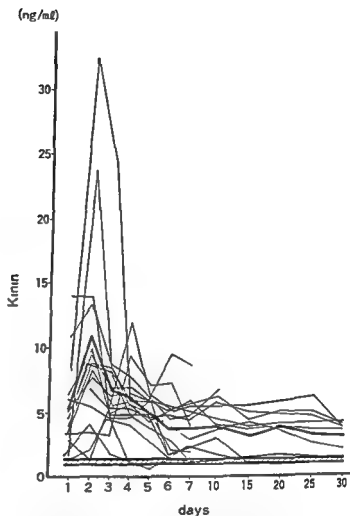


Fig 2 Changes in kinin levels in cubital vein blood in 16 surviving patients. Mean values are shown by a thick line and individual patients are represented by thin lines. A cross hatched zone indicates normal range (mean  $\pm$  SEM).

two thirds of the patients exhibited a reduced kininogen level on the first day. A further decrease was observed on the second day ( $2.4 \pm 0.3$   $\mu\text{g/ml}$ ). Thereafter kininogen values tended to recover, reaching near normal levels 10 or 15 days from the onset of the infarction. Nine of the 16 patients were followed up to 30 days and of these six exceeded the normal kininogen level while two remained below normal.

**Kinin.** Alterations in the kinin levels in cubital vein blood sampled in surviving patients are shown in Fig 2. Baseline kinin values from five normal individuals were established as  $1.2 \pm 0.1$   $\text{ng/ml}$  and are indicated by the cross hatched area. Except for one, all patients exhibited kinin elevation on the first day after the infarction followed by a further significant increase on the second day to  $10.1 \pm 2.0$   $\text{ng/ml}$ . Subsequently, kinin levels tended to decrease but the mean value remained above normal even 30 days after





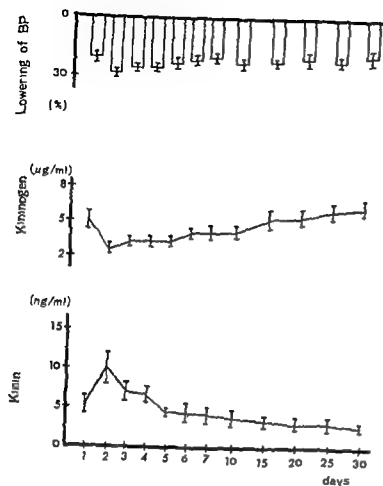


Fig 4 Changes in blood pressure kininogen and kinin in the 16 surviving patients (mean  $\pm$  SEM)

Table 1 Correlations between changes in kinin system substances and alterations in hemodynamics

|                             | Kininogen | Kinin  |
|-----------------------------|-----------|--------|
| Lowering blood pressure     | -0.46     | 0.30   |
| Cardiac output              | -0.15     | 0.05   |
| Total peripheral resistance | 0.35*     | -0.41* |
| Circulation time (arm-ear)  | -0.41     | 0.59*  |

p < 0.05

p < 0.01

circulation time ( $r = -0.41$ ,  $p < 0.01$ ) Significant positive correlation was also seen between kininogen and total peripheral resistance ( $r = 0.35$ ,  $p < 0.05$ ) There were significant correlations of  $r = 0.30$  ( $p < 0.05$ ) between kinin and lowering of blood pressure and of  $r = -0.41$  ( $p < 0.01$ ) between kinin and total peripheral resistance Significant positive correlation was also observed between kinin and circulation time ( $r = 0.59$ ,  $p < 0.01$ )

These data suggest that kinin system sub

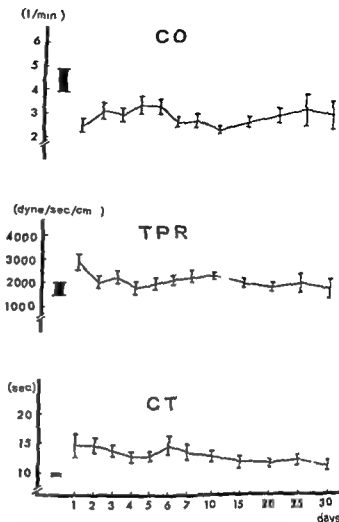


Fig 5 Changes in cardiac output (top) total peripheral resistance (middle) and circulation time (bottom) in nine surviving patients (mean  $\pm$  SEM) Solid columns in each panel indicate normal ranges (mean  $\pm$  SEM)

stances activated after the onset of myocardial infarction might play a role in dilating peripheral vessels and thus prolonging the circulation time

**II Changes in kinin system substances in non survivors** Of the seven patients who failed to survive more than 2 days after the onset of acute myocardial infarction, two died on the first day, one on the second day and four on the third day Four out of these seven patients died of cardiogenic shock and three of congestive heart failure

Blood samples were taken more than once a day Sequential determinations of kininogen and kinin blood levels from the onset of infarction until death are indicated in Fig 6 For comparison kininogen and kinin levels measured within 3 days after the onset in the survivors are also shown

Kininogen levels in the non survivors were  $40 \pm 0.3 \mu\text{g/ml}$ , which was lower than in normal

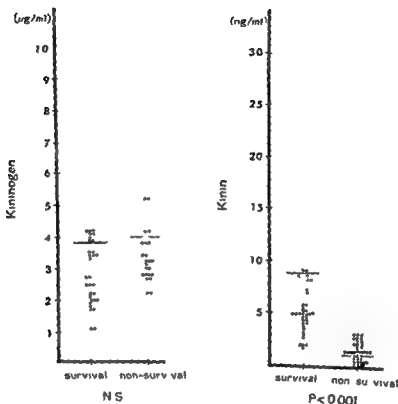


Fig 6 Blood kininogen (left panel) and kinin (right panel) levels in surviving as well as non surviving patients within 3 days from the onset

controls but no significant difference was noted when compared to surviving patients ( $3.8 \pm 0.3$   $\mu\text{g/ml}$ ). On the other hand there was a dramatic difference in kinin levels between survivors and non survivors. Thus in survivors the mean kinin level within 3 days of infarction was  $8.7 \pm 0.9$   $\text{ng/ml}$  significantly higher than normal. In contrast kinin levels in the non survivors remained within normal limits ( $1.0 \pm 0.1$   $\text{ng/ml}$ ). Thus while a reduction in kininogen was associated with increased kinin levels in survivors no increase in kinin was observed in the non survivors in spite of decreased kininogen levels.

#### Discussion

It has been proposed that plasma kinin plays an important role in shock states secondary to hemorrhage, endotoxin, anaphylaxis, pancreatitis, burns and trauma. Kinin has also been implicated in cardiogenic shock and is thought to be an important factor in death from acute myocardial infarction. Our previous study of coronary artery ligation in dogs demonstrated that kinin levels in coronary sinus blood

increased following coronary occlusion and correlated with decreased myocardial contractility and elevated left ventricular end diastolic pressure. When dogs were pretreated with aprotinin (Trasylol, an inhibitor of the kinin releasing enzyme) the post ligation increase in kinin and associated hemodynamic alterations were inhibited. We surmised that release of myocardial kinin following coronary artery ligation might contribute to a negative inotropic action which could be a factor in the development of cardiogenic shock. However these observations were limited to very short term experiments. In this study, we investigated changes in kinin system substances in patients with acute myocardial infarction. An unexpected observation of this study was that kinin did not increase in patients who died of pump failure although kininogen levels decreased. There was no correlation in these patients between the kinin measurements and hemodynamic indices such as blood pressure and cardiac output (data not shown). On the other hand surviving patients exhibited a decrease in kininogen as well as an increase in kinin, both of

which were significantly related to a lowering of blood pressure, decreased total peripheral resistance, and prolongation of circulation time during the early stage of the infarction. These observations indicated that kinin system substances might not play a major role in the pathogenesis of shock or heart failure following acute myocardial infarction.

We considered possible reasons for the observed differences in kininogen and kinin changes between surviving and non surviving patients. The reasons why no kinin elevation was found in non survivors, in spite of decreased kininogen, might be attributed to the fact that (1) kinin released in the ischemic myocardium may not be adequately washed out from the ischemic zone because of severe regional hypoperfusion, (2) the released kinin may be rapidly inactivated by the lung or through potent kininase activity in the circulating blood, (3) a low kininogen level in non survivors may be due to impairment of its synthesis by the liver, (4) there was interaction with drugs used for treatment of the shock state. As to the first theory, low kininogen and unchanged kinin levels were observed even before perfusion pressure had been above the shock level in non survivors and no correlation was obtained between kinin system substances and blood pressure. Thus this cannot be considered. As to the third possibility, liver damage and/or hypoproteinemia were not always seen in these patients. Thus this hypothesis appears unreasonable. Regarding the fourth proposition, norepinephrine, dopamine, digitalis, furosemide or steroids were administered to patients to maintain the blood pressure, but these changes in blood kinin system substances were also observed in samples taken before drug treatment. We therefore believe that the low kininogen and normal kinin levels found in non survivors might be due to the high kininase activity in the lung or in the circulating blood.

It is well known that strong kininase activity exists in the lung and more than 80 per cent of the blood kinin is destroyed while passing through the pulmonary circulation.<sup>16</sup> Also, half life of synthetic bradykinin in blood was shown to be within 0.5 minute.<sup>17</sup> Our recent study<sup>18</sup> indicated that kininase activity decreased after acute myocardial infarction in survivors but remained normal in patients who died of shock. A normal kininase

activity might lead to rapid and significant inactivation of kinin. Thus, the observed changes in kinin system substances in non survivors could be attributed to kininase activity in circulating blood.

There are discrepancies between our observations of kinin in shock states and those of other investigations. Sicuteri and colleagues<sup>1</sup> reported that blood kininogen levels decreased in the initial several days after acute myocardial infarction and that such a decrease in kininogen was more pronounced in non survivors corresponding to a significant lowering of blood pressure. They concluded that kinin system substances are responsible for the genesis of cardiogenic shock. Dzizinski and co workers<sup>4</sup> compared kininogen levels in patients with an inactive form of coronary insufficiency, angina pectoris, acute myocardial infarction and cardiogenic shock, and found that kininogen levels depended on the severity of the diseases. Wieggershausen and associates<sup>5</sup> also deduced that kinin is one of the causes of cardiogenic shock from their observation of decreases in kininogen in patients with acute myocardial infarction.

Thus most of the authors concluded that the activated kinin induced hypotension which might be a cause of shock. This was based upon the observations that kininogen decreased in the initial stage of myocardial infarction and that changes were more prominent in cardiogenic shock. Our observations on the other hand are in accord with that of Wilson and colleagues<sup>10</sup> who failed to find significant differences in kininogen between shock and non shock patients.

It is necessary to emphasize that most of the above conclusions are based on measured decreases in kininogen levels with only indirect estimates of increases in kinin levels. As already mentioned, our recent study<sup>18</sup> indicates that kininase activity was low in patients without shock in myocardial infarction whereas strong normal kininase activity was found in patients who died of shock. These observations would indicate that the released kinin might remain longer in the blood of survivors than in the blood of non survivors. This suggests that the kinin released in patients with infarction might actually be beneficial rather than a cause of cardiogenic shock.

Recently vasodilator therapy by reducing the afterload of the heart,<sup>19, 20</sup> has been reported to be

a valuable mode of treatment during cardiogenic shock or congestive heart failure following acute myocardial infarction. As kinin appears to have a potent coronary and peripheral vasodilating action, the beneficial effects of endogenously released kinin can be considered in patients with acute myocardial infarction.

Kinin has also recently been proposed to be a mediator of prostaglandins which regulate coronary blood flow.<sup>21,22</sup> Further studies might clarify these mechanisms in acute myocardial infarction.

# Summary

Kinin is known to have potent pain producing and hypotensive actions and has been suggested as one of the causes of chest pain and shock in acute myocardial infarction. Since most of the previous reports<sup>1</sup> have been based on measurements of kininogen, the inactive precursor of kinin, peripheral blood kinin as well as kininogen was measured in this study. Kinin and kininogen levels were determined over a period of one month or until death from the onset in 23 cases of acute myocardial infarction, along with simultaneous measurements of hemodynamic indices. Sixteen of the 23 cases survived more than one month, and seven patients died of pump failure within 3 days of the infarction. In the survival group, increased kinin and decreased kininogen levels were observed in the initial stage, reaching a maximal change on the second day. The alterations in kinin levels were significantly correlated with concomitant lowering of blood pressure, decreased total vascular resistance, and prolongation of circulation time. In the non-survival group, there was no increase in kinin levels in spite of a decrease in kininogen. Accordingly, no significant correlation was found between kinin and hemodynamic changes. The lack of change in kinin in the latter group was thought to account for the strong kininase activity. Thus, these data indicate that kinin is not the cause of cardiogenic shock. Rather, the increased kinin level observed in survivors might indicate beneficial vasodilation effects, possibly by increasing coronary flow and reducing the afterload of the left ventricle.

# REFERENCES

1. Page D L, Caulfield J B, Kastor J A, DeSanctis R W and Sanders C A. Myocardial changes associated with cardiogenic shock. *N Engl J Med* 285 133 1971.
2. Braunwald E, and Maroko P R. The reduction of infarct size—an idea whose time (for testing) has come. *Circulation* 50 206 1974.
3. Scuteri F, Franchi G, Del Bianco P L, and Del Bene E. A contribution to the interpretation of shock and pain in myocardial infarction. *Malattie Cardiovascolari* 8 343 1967.
4. Attar S M A, Tingey H B, McLaughlin J E, and Cowley H A. Bradykinin in human shock. *Surg Forum* 18 46 1967.
5. Wiegandhausen B, Hennighausen G, Klausch B, Korber H G, and Hauzeur F. Plasma kininogen level in myocardial infarction. In Scuteri F, Rocha e Silva M, and Back N, editors. *Bradykinin and related kinins: Cardiovascular, biochemical, and neural actions*. Advances in Experimental Medicine and Biology vol. 8. New York 1970. Plenum Press, p 221.
6. Dziznuk A A, and Kumov A D. Blood kinin system in pathogenesis and clinic of ischemic heart disease. *Cor Vasa* 14 9 1972.
7. Scuteri F, Antonini E M, Del Bianco P L, Franchi G, and Curradi C. Prekallikrein and kallikrein inhibitor in plasma of patients affected by recent myocardial infarction. In Back N, and Scuteri F, editors. *Vasoproteid chemistry, pharmacology and pathology*. Advances in Experimental Medicine and Biology vol. 21. New York, 1972. Plenum Press, p 445.
8. Kumura H, Hashimoto K, Furukawa S, and Haya kawa H. Changes in bradykinin level in coronary sinus blood after the experimental occlusion of a coronary artery. *AM HEART J* 85 635 1973.
9. Hashimoto K, Furukawa S, Hirose M, and Haya kawa H. Changes in bradykinin level in coronary sinus blood after experimental coronary occlusion and their relationships to hemodynamic changes. *Singapore Med J* 14 356 1973.
10. Brocklehurst W E, and Zeithin I J. Determination of plasma kinin and kininogen levels in man. *J Physiol* 191 417 1967.
11. Abe K, Watanabe M, Kumagai N, Mouri T, Seki T, and Yoshinaga K. Estimation of kinin in peripheral blood in man. *Tohoku J Exp Med* 89 103 1966.
12. Webster M E, and Clark W R. Significance of the callicrein-callicidinogen-callicidin system in shock. *Am J Physiol* 197 406 1959.
13. Brocklehurst W E, and Lahiri S C. The production of bradykinin in anaphylaxis. *J Physiol (Lond)* 160 15 1962.
14. Thal A P, Kobold E E, and Hollenberg M J. The release of vasoactive substances in acute pancreatitis. *Am J Surg* 105 108 1963.
15. Back N, Wilkens H, and Steger R. Proteinases and proteinase inhibitors in experimental shock states. *Ann N Y Acad Sci* 146 491 1968.
16. Ferreira S H, and Vane J R. The disappearance of bradykinin and edosin in the circulation and vascular beds of the cat. *Br J Pharmacol. Chemother* 30 425 1967.
17. McCarthy D A, Potter D E, and Nicolaides E D. An *in vivo* estimation of the potencies and half-lives of synthetic bradykinin and kallidin. *J Pharmacol Exp Ther* 148 117 1965.
18. Hashimoto K, Wanka J, Kohn R N, Wilkens H J.

We are grateful to Dr Nathan Back, State University of New York at Buffalo, and Dr Emanuel Meerbaum, Cedars-Sinai Medical Center, Los Angeles, for their valuable assistance in the preparation of this paper.

- Steger R and Back N The vasoactive peptide kinin system in acute clinical cardiac diseases in Scuteri F Back N and Haberland G L editors *Kinins pharmacodynamics and biological roles Advances in Experimental Medicine and Biology* vol 70 New York and London 1976 Plenum Press p 245
- 19 Wilson R F Chiscano A D and Quadros E Some observations on 58 patients with cardiac shock *Anesth Analg* 46 764 1967
- 20 Chatterjee K Parmley W W Ganz W Forrester J Walinsky P Crexells C and Swan H J C Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction *Circulation* 48 1183 1973
- 21 Awan N A Amsterdam E A Vera E DeMaria A N Miller R H and Mason D T Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction *Circulation* 54 761 1976
- 22 Afonso M Bandow G T and Rowe G G Indomethacin and the prostaglandin hypothesis of coronary blood flow regulation *J Physiol* 241 299 1974
- 23 Needleman P The synthesis and function of prostaglandins in the heart *Fed Proc* 35 2376 1976

## Case reports

### *Chlamydia trachomatis* endocarditis

Johanna M van der Bel Kohn MD  
Chatchai Watanakunakorn MD \*\*  
Max G Menefee MD PhD \*  
Herbert D Long MD \*\*\*  
Richard Duter MD \*  
Cincinnati Ohio

The clinical diagnosis of infective endocarditis may be difficult to ascertain especially if multiple blood cultures are negative and complicated clinical circumstances further mask the actual pathologic process.

The true incidence of negative blood cultures in the presence of active infective endocarditis is not known since many factors are involved. The reported incidence varies from 0 to 40 per cent. Papers from Great Britain and Australia mention negative blood cultures accompanying endocarditis due to *Coxiella burnetii*. Blood cultures were also negative in a Scottish report of two cases of active infective endocarditis due to *Chlamydia psittaci* occurring on previously damaged valves.

The major purposes of this paper are (1) to report a case of *Chlamydia trachomatis* endocarditis and to underscore the specialized modalities which may be needed to establish the diagnosis (2) to bring to the attention a new echocardiographic finding.

The patient was a 25 year old woman of 30 weeks gestation who presented with fever and multiple negative blood cultures and died after a short fulminating clinical course. Studies performed after death allowed clarification of a puzzling clinical picture.

From the Department of Pathology, the Department of Internal Medicine, Division of Infectious Diseases, and the Division of Cardiology, University of Cincinnati College of Medicine, Cincinnati, Ohio. Received for publication May 6, 1978.

Accepted for publication May 26, 1978.

Reprint requests: Dr. Johanna M. van der Bel Kohn, Department of Pathology, Room 1376, University of Cincinnati College of Medicine, Cincinnati, Ohio 45229.

Department of Pathology

Department of Internal Medicine, Division of Infectious Diseases, Division of Cardiology

#### Case report

A 25-year-old pregnant woman of 30 weeks gestation was admitted to the Cincinnati General Hospital on August 21, 1976 with a five day history of discomfort in the left side of the neck and left shoulder. One day prior to admission she experienced nausea, vomiting, malaise and feverishness. She had noted a malodorous vaginal discharge on several occasions but her pregnancy had been otherwise uncomplicated. She denied cough, abdominal discomfort, headache, dyspnea or skin rash. The past medical history was unremarkable and she was on no medications.

Admission physical examination revealed blood pressure of 132/84 mm Hg, pulse 120/minute, respirations 20/minute and temperature 103°F (39.4°C). The skin and mucous membranes were unremarkable. No nuchal rigidity was present. The lung fields were clear. A Grade 1/6 systolic ejection murmur was audible in the second and third left intercostal spaces and a ventricular gallop rhythm was present. The uterus was approximately thirty weeks gestational size with fetal heart tones of 190 per minute. A small amount of white cervical discharge was present. Neurological examination was unremarkable.

Initial laboratory data included: white blood count 2000/mm<sup>3</sup>, with 58 per cent segmented neutrophils, 28 per cent band forms, 11 per cent lymphocytes and 3 per cent monocytes; hemoglobin 10.9 Gm per cent; hematocrit 34 per cent; and erythrocyte sedimentation rate 88 mm/hour (Westergren). The BUN, electrolytes and SMA 12/80 were normal. Urinalysis showed 6 to 8 white blood cells per high power field and no organisms on gram stain. X rays of the chest and left shoulder as well as the electrocardiogram were unremarkable. Data subsequently obtained included: antistreptolysin O titer less than 166 Todd units; negative latex fixation test for rheumatoid factor; negative intermediate strength purified protein derivative tuberculin test; Histoplasma complement fixation titer 1:8 and negative antinuclear antibody test. Four sets of aerobic and anaerobic blood cultures were negative. Urine culture was negative and culture of the cervical discharge grew only a few *Staphylococcus epidermidis*. An echocardiogram demonstrated a posterior pericardial effusion with no abnormalities of the aortic valve and no diastolic fluttering of the mitral valve (Fig. 1).

On the second hospital day a to and fro aortic murmur was suspected but subsequently a loud triphasic pericardial friction rub became audible and no separate murmur could be detected. A therapeutic trial of salicylates produced initial

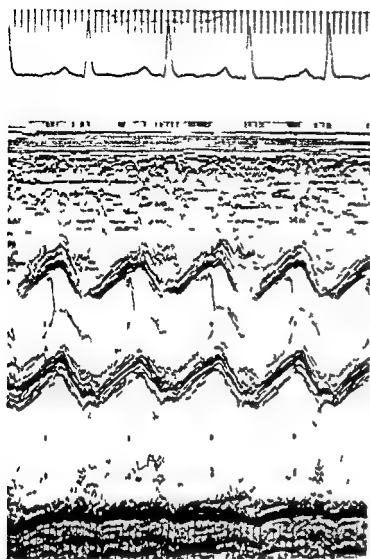


Fig 1 Echocardiogram at the aorta and left atrium performed early in the patient's hospital course. The aortic valve leaflets are thin and the aortic walls are not abnormally thickened.

subjective improvement but chest pain subsequently returned. On September 1 Prednisone in a dose of 60 mg per day was begun with a presumptive diagnosis of idiopathic pericarditis.

Three days later the patient was found unconscious but awoke several minutes later demonstrating a transient right-sided hemiparesis. She had a blood pressure of 130/50 mm Hg with no paradoxical arterial pulse, normal venous pressure and clear lung fields. The friction rub persisted. Arterial blood gases showed a pH of 7.34,  $pCO_2$  22, and  $pO_2$  96 while the patient was receiving nasal oxygen at 3 liters per minute. The electrocardiogram showed sinus tachycardia and ST segment depression in the inferior leads. Chest radiogram showed enlargement of the cardiopericardial silhouette. Lumbar puncture revealed 40 red blood cells per mm<sup>3</sup> of cerebrospinal fluid. A second echocardiogram demonstrated both anterior and posterior pericardial effusions, normal mitral and aortic valve echoes, and an abnormal dense echo in the region of the aortic root and left atrium which moved parallel with the posterior aortic wall (Fig 2). This echo could not be eliminated by changes in gain or minor changes in transducer angulation. Consideration of pericardiocentesis or aortic

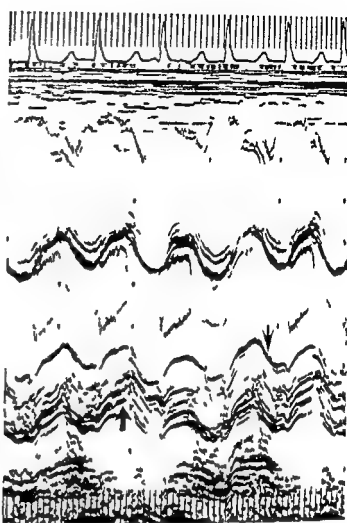


Fig 2 Repeat echocardiogram at the left atrium and aorta performed one day before death. The posterior aortic wall (thin arrow) is well visualized. An abnormal dense echo (thick arrow) with motion parallel to the aortic wall is present. The aortic leaflets show systolic fluttering but are not abnormally thickened.

angiography was postponed pending possible evacuation of the uterus.

The patient became increasingly dyspneic and developed signs of pulmonary edema. A Swan Ganz catheterization revealed the following pressures: right ventricle 65/3, pulmonary artery 63/17, and pulmonary wedge pressure of 96. Cardiac arrest occurred and the patient was successfully resuscitated. Fetal heart tones were no longer audible. Following several more arrests, she could no longer be resuscitated and she died on September 7, 1976.

**Necropsy** The necropsy was performed 26 hours after death. The major pathologic findings were confined to the heart except for a hemorrhagic cortical infarction in the right cerebral hemisphere and recent acute bronchopneumonia of a few days' duration. The pericardial sac contained 550 ml of clotted blood. The visceral epicardial surface was diffusely covered by a thick shaggy fibrinous exudate which was most marked surrounding the root of the great vessels. The heart weighed 520 Gm and showed left ventricular hypertrophy. There was no evidence of any congenital cardiac anomaly or healed rheumatic valvular disease. A vegetation with finger-like projections (Fig 3) sat on the ventricular surface of the



Fig 3 View of left ventricular outflow tract and the opened ascending aorta with the origin of major branches at the arch. At the root of the aorta the intact right and non coronary cusps are clearly visible. The left coronary cusp shows just below its turn the vegetation with the finger like projections and an oval shaped ring abscess. The gaping opening in the endocardial surface is located immediately below the left coronary cusp with its vegetation and to the left of the ring abscess. Ao = aorta ascending Rab = ring abscess

left coronary cusp of the aortic valve. Just caudal to it the cusp showed a small probe patent perforation. Immediately below the base of this was a large slit like gaping and clot filled opening led into a cavity of  $1.5 \times 0.5$  cm (Fig 3). This cavity was contiguous with an aortic ring abscess of  $2 \times 2 \times 1$  cm (Fig 4) in a cephalad direction while caudally it extended between the endocardial surfaces of the anterior mitral leaflet. Here it continued into three bulging lesions which protruded from the atrial surface of the base of the mitral cusp (Figs 5 and 6). They measured up to  $1 \times 1.5$  cm in largest diameter. The destructive process also involved part of the commissure between the left and non-coronary cusps so that a communication existed between the sinuses of Valsalva of each of these cusps. The contour and delicate structure of the non-coronary and right coronary cusps were preserved. Blood clot filled a rupture site of the sinus of Valsalva behind the left coronary cusp (Fig 6). This explained the leakage of blood into the pericardial sac which appeared to have been late in the patient's course. The aortic valve endocarditis was further complicated by acute infarction of the anterior and posterior papillary muscles of the left ventricle. Routine culture of the

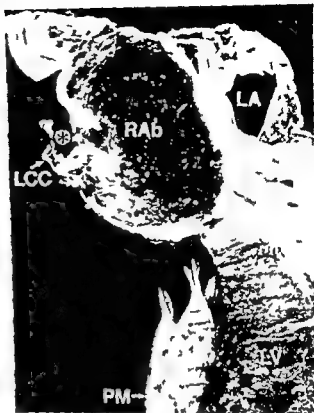


Fig 4 Section through aortic valve with ring abscess left atrium and left ventricular wall with infarcted papillary muscle. The abscess reaches cephalad and above the upper margin of the cusps of the aortic valve = sinus of Valsalva. LA = left atrium LCC = left coronary cusp LV = left ventricle PM = papillary muscle Rab = ring abscess

vegetation and ring abscess yielded growth only of contaminants. Histologic examination revealed an acute inflammatory necrotizing process at the aortic ring. Cloudy amorphous material in the aortic valve vegetation was surrounded by macrophages polymorphonuclear leucocytes and marked edema.

Grocott and Ziehl Nielsen stains were negative. The Gram stain and numerous others including the Macchiavello and Giménez stains were equivocal. Giemsa and indirect fluorescent stains of formalin fixed sections were nonrevealing. The fibrinous pericarditis was organizing and consistent with a few weeks age. Ultrastructural studies were performed on one of the finger like projections of the vegetation.

For electron microscopy formalin fixed tissue was washed in cacodylate buffer, refixed in 4 per cent cacodylate buffered glutaraldehyde, post osmicated, dehydrated and embedded in epoxy resin. Thin sections were photographed in a Siemens Elmiskop 101 electron microscope.

Considerable autolysis was exhibited by the cells making up the vegetation with the host cells being more degenerated than either the inter or intracellular organisms. Remnants of cytoplasmic vacuoles were found in which were located various stages in the developmental cycle of the contained organisms (Fig 7). Three different forms of the organism could





Fig 5 Inflow tract of left ventricle Three bulging lesions protrude from the atrial surface of the basal portion of the anterior mitral leaflet AL = anterior leaflet of mitral valve APM = anterior papillary muscle LA = left atrium

be distinguished The Initial Body was characterized by a uniform dispersal of ribosomes and little or no condensation of chromatin these represented the pre division stage of development after entry into the cell (Fig 8) The Initial Body as well as all other stages was surrounded by a plasma membrane plus a rudimentary cell wall (Fig 8) The Intermediate Body contained dispersed ribosomes and an increasingly obvious condensation of chromatin (Fig 9) The Elementary Body was marked by dense condensation of all cell contents and a reduction in overall dimension (Fig 10)

**Serology** Two retrieved serum samples which had been collected on August 23 and August 28 15 and 10 days pre-mortem respectively were tested by the microimmunofluorescence method for antibodies to *Chlamydia trachomatis* A thirty two fold rise in the IgM antibody and a sixteenfold rise in the IgG antibody to immunotype F antigen were demonstrated (Table I) There was cross reaction with type G antigen The serum sample collected on August 28 (10 days pre-mortem) also contained cross reacting IgM antibody to types E D and L, and IgG antibody to types H I K E D and L There was a stable IgG antibody titer of 1:64 but no IgM antibody to type J antigen The IgG antibody to type J antigen also cross reacted with type C antigen

Both serum samples were tested for antibody to *Coxiella*



Fig 6 Sagittal section through left ventricle and left atrium demonstrating left ventricular in and outflow tracts The destructive and extensive nature of the process is evident and also the contiguity and relationship between the lesions in the aortic valve the aortic wall and the anterior leaflet of the mitral valve The rupture site of the sinus of Valsalva is also clearly visible Ao = ascending aorta H = hemorrhage due to rupture of sinus of Valsalva LA = left atrium LV = left ventricle PPM = posterior papillary muscle R = rupture site sinus of Valsalva of left coronary cusp

*burnetti* by the microagglutination and microimmunofluorescence methods The results were negative Complement fixation tests for antibody to *Chlamydia psittaci* and *Chlamydia trachomatis* were performed on both serum samples but the serum was anticomplementary

## Comments

The *Chlamydiae* are a group of organisms that have a rudimentary bacteria like cell wall and multiply by binary fission They contain both DNA and RNA but are unable to sustain growth outside an animal cell They are also susceptible to a number of antimicrobial agents Thus their obligate intracellular growth is more like those of viruses but their biochemistry and molecular structure are more like bacteria There are presently two species in the family *Chlamydiaceae*

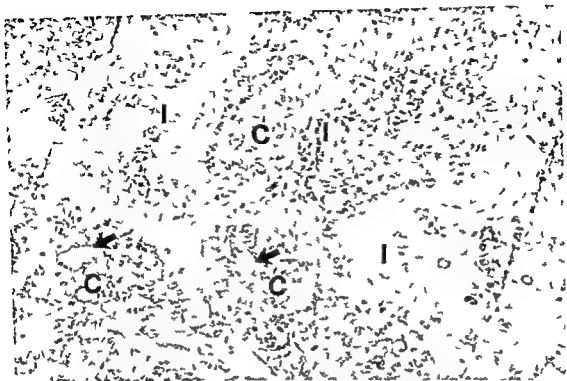


Fig 7 Survey view of host cells (C) demonstrating partial autolysis and Chlamydia (illustrated at arrows) in different developmental stages. Interstitial fibrin is indicated by I (Original magnification  $\times 6750$ )



Fig 8 Initial Bodies (IB) are characterized by relatively large size as compared to the Intermediate Body (IF) and by the paucity of chromatin. Each organism is surrounded by a plasma membrane (thin arrow) and by an external rudimentary cell wall (thick arrow) (Original magnification  $\times 43800$ )



Fig 5 Inflow tract of left ventricle Three bulging lesions protrude from the atrial surface of the basal portion of the anterior mitral leaflet AL = anterior leaflet of mitral valve APM = anterior papillary muscle LA = left atrium

be distinguished. The Initial Body was characterized by a uniform dispersal of ribosomes and little or no condensation of chromatin; these represented the pre division stage of development after entry into the cell (Fig 8). The Initial Body as well as all other stages was surrounded by a plasma membrane plus a rudimentary cell wall (Fig 8). The Intermediate Body contained dispersed ribosomes and an increasingly obvious condensation of chromatin (Fig 9). The Elementary Body was marked by dense condensation of all cell contents and a reduction in overall dimension (Fig 10).

**Serology** Two retrieved serum samples which had been collected on August 23 and August 28, 15 and 10 days pre-mortem respectively were tested by the microimmunofluorescence method for antibodies to *Chlamydia trachomatis*. A thirty two fold rise in the IgM antibody and a sixteen fold rise in the IgG antibody to immunotype F antigen were demonstrated (Table I). There was cross reaction with type G antigen. The serum sample collected on August 28 (10 days pre-mortem) also contained cross reacting IgM antibody to types III D and L and IgG antibody to types H I K E D and L. There was a stable IgG antibody titer of 1:64 but no IgM antibody to type J antigen. The IgG antibody to type J antigen also cross reacted with type C antigen.

Both serum samples were tested for antibody to *Coxiella*



Fig 6 Sagittal section through left ventricle and left atrium demonstrating left ventricular in and outflow tracts. The destructive and extensive nature of the process is evident and also the contiguity and relationship between the lesions in the aortic valve, the aortic wall and the anterior leaflet of the mitral valve. The rupture site of the sinus of Valsalva is also clearly visible. Ao = ascending aorta H = hemorrhage due to rupture of sinus of Valsalva LA = left atrium LV = left ventricle PPM = posterior papillary muscle R = rupture site sinus of Valsalva of left coronary cusp

*burnetti* by the microagglutination and microimmunofluorescence methods. The results were negative. Complement fixation tests for antibody to *Chlamydia psittaci* and *Chlamydia trachomatis* were performed on both serum samples but the serum was anticomplementary.

## Comments

The *Chlamydiae* are a group of organisms that have a rudimentary bacteria like cell wall and multiply by binary fission. They contain both DNA and RNA but are unable to sustain growth outside an animal cell. They are also susceptible to a number of antimicrobial agents. Thus their obligate intracellular growth is more like those of viruses but their biochemistry and molecular structure are more like bacteria. There are presently two species in the family *Chlamydiaceae*

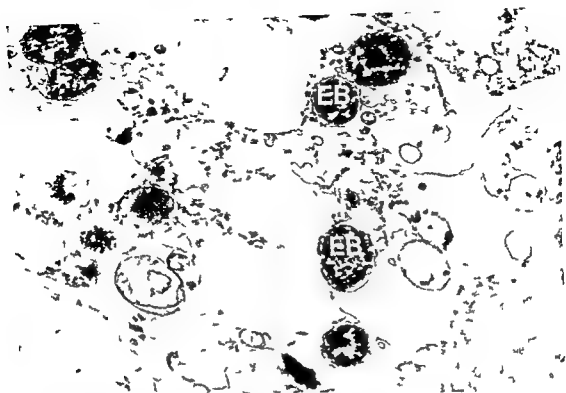


Fig. 10 The Elementary Body (EB) is seen intermixed with cell debris. Some filaments of fibrin are in the lower right corner. This is the infective form which is taken up by a cell to begin the reproductive cycle. Note the thin wavy cell wall surrounding each organism. (Original magnification  $\times 2560$ )

Table 1 Serum antibody to *Chlamydia trachomatis* by the microimmunofluorescent antibody test\*

| Nature of antibody | Date of serum | Immunotype antigen of <i>Chlamydia trachomatis</i> |    |   |    |    |   |   |     |    |   |     |     |
|--------------------|---------------|--|----|---|----|----|---|---|-----|----|---|-----|-----|
|                    |               | C  | J  | A | H  | I  | K | B | E   | D  | L | L   | L   |
| IgM                | 8/23/ 6       | —  | —  | — | —  | —  | — | — | 8†  | —  | — | —   | 8   |
|                    | 8/28/76       | —  | —  | — | —  | —  | — | — | 128 | 64 | — | 128 | 512 |
| IgG                | 8/23/ 6       | 3°   | 64 | — | —  | —  | — | — | —   | —  | — | —   | 8   |
|                    | 8/28/76       | 16   | 64 | — | 3° | 16 | 8 | — | 128 | 16 | — | 256 | 256 |
| IgM IgA<br>-IgG    | 8/23/ 6       | 16   | 64 | — | —  | 8  | 8 | — | 8   | —  | — | —   | 8   |
|                    | 8/28/ 6       | 16   | 64 | — | 3° | 3° | — | — | 128 | 64 | — | 256 | 64  |

\* Kindly performed by Sa-pun Wang, M.D., Department of Pathology, School of Public Health and Community Medicine, University of Washington, Seattle, Wash.

— = < 8

† = reciprocal of the serum dilution

suspected as the causative organism and tissue cultures were not performed. Complement fixation test for antibody to *Chlamydia psittaci* was of no value because the patient's serum proved to be anticomplementary. The equivocal results of special stains which are usually utilized to demonstrate chlamydia were probably due to autolysis and demanded more sophisticated methods of examination. The subsequent finding of *Chlamydia* in the vegetation by electron

microscopy warranted further in depth serologic studies.

The thirty-two fold rise (from 1:16 to 1:512) in the patient's IgM antibody to immunotype F *Chlamydia trachomatis* during her brief illness indicates that she was in the acute stage of *Chlamydia trachomatis* infection most likely due to immunotype F organism. It is known that antibody to type F antigen commonly cross reacts with type G antigen.\* The serum sample

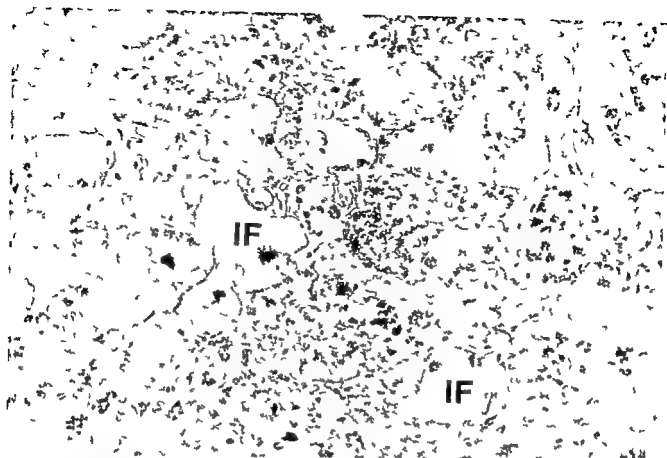


Fig 9 Intermediate Bodies (IF) have dispersed ribosomes and the beginning condensation of chromatin (Original magnification  $\times 17,300$ )

namely *Chlamydia psittaci* which primarily produced diseases in mammals or birds and can be transmitted to man resulting in psittacosis and ornithosis, and *Chlamydia trachomatis* which causes primary diseases in humans such as trachoma, inclusion conjunctivitis, lymphogranuloma venereum, urethritis, and cervicitis.<sup>9</sup> One recent report also implicated *Chlamydia trachomatis* in a distinctive pneumonia syndrome in black infants 4 to 24 weeks of age.<sup>10</sup>

All Chlamydiae are characterized by complex cycles of multiplication.<sup>11-12</sup> Electron microscopic studies of appropriately infected tissue culture cells show that the first stage of infection consists of uptake of an Elementary Body (Fig 10) by the host cell into a cytoplasmic vacuole.<sup>13</sup> A group of vacuoles then coalesce and form an inclusion body containing many organisms which have transformed their structure into that of the Initial Body (Fig 8). The Initial Body undergoes one or more divisions and then, following the last division, the organisms begin to condense into Intermediate Bodies (Fig 9), and finally are released into the intercellular space as Elementary Bodies which can then begin a new cycle of infection. In our present case, it was not possible

to locate a membrane surrounding all of the inclusion bodies. One of the distinguishing characteristics of *Chlamydia psittaci* is the disappearance of the inclusion body membrane during the late stage of division.<sup>14</sup> Since the host cells in the present case were extensively autolyzed, the lack of such a membrane has little diagnostic significance. Occasional giant forms which appeared to reproduce by budding rather than by division were reported in *Chlamydia trachomatis* growing in tissue culture.<sup>15</sup>

The diagnosis of *Chlamydia trachomatis* endocarditis in our patient was retrospective. Further diagnostic procedures were performed after the usual causes of infective endocarditis were excluded. The unusual finger-like vegetations reminded one of us (C.W.) of similar findings in two previously reported cases of *Chlamydia psittaci* endocarditis.<sup>4</sup> However, these occurred on previously damaged valves and in patients who both had pulmonary psittacosis as well. Our patient had no exposure to birds and there was no evidence of pulmonary psittacosis. In addition, her active infective endocarditis occurred on a previously normal aortic valve. At the time the autopsy was performed, Chlamydiae were not

Since *Chlamydia trachomatis* genital infections are widespread it is conceivable that many cases of *Chlamydia trachomatis* endocarditis remain undiagnosed. The micro immunofluorescence test for antibody to *Chlamydia trachomatis* is a valuable diagnostic tool. In a patient with a clinical picture compatible with infective endocarditis and negative blood cultures a four fold or more rise in IgM antibody to *Chlamydia trachomatis* is highly suggestive of *Chlamydia trachomatis* infection. If surgery is carried out the diagnosis can further be confirmed by tissue culture for chlamydia immunofluorescence staining and ultrastructural examination of the affected tissue.

The ability of the echocardiogram to delineate valvular vegetations is well recognized. We have been unable to find previous reports of echocardiographic abnormalities associated with an aortic valve ring abscess. The unusual echo from the region of the aortic root and left atrium which developed during the course of this patient's illness is similar to that reported in several other circumstances. The presence of an abnormal echo with motion parallel to the posterior aortic wall along with simultaneous visualization of normal valve leaflets is consistent with aortic dissection. The specificity of this pattern however has been questioned by Brown and colleagues who reported similar findings in normal subjects and suggested that echos were being reflected from both sides of the aortic-left atrial wall. Other sources of an abnormal echo from the region of the aortic root and left atrium include effusion in the transverse sinus of the pericardium and echos from the left atrial insertion of the pulmonary veins. However motion of the abnormal echo parallel to the aortic wall is not to be expected in these cases. The failure to eliminate the abnormality with changes in gain or transducer angulation militates against mere technical problems.

Examination of the pathological specimen in this case (Fig 4 and diagram Fig 11) illustrates that the echobeam in a plane which would pass through the aortic valve leaflets would next pass through the valve ring abscess before entering the left atrium. We feel therefore that in this case the abnormal echocardiographic finding represents echocardiographic detection of the abscess. The possibility that the abnormal echo was reflected from the dilated sinus of Valsalva must

be considered but the relative locations of the sinus and the abscess in the projected path of the echobeam favors our former interpretation.

The echocardiogram of this patient did fail to demonstrate vegetations on the aortic valve leaflets. This was probably due to the location of the vegetations on and restricted to the left coronary leaflet since this leaflet is not routinely visualized by current techniques. In retrospect the scan from the tip of the mitral valve to the aorta did reveal some dense echos from the region of the base of the mitral valve (Fig 12). This probably represents the vegetations found at the base of the anterior mitral leaflet (Figs 5 and 6).

The degree of destructiveness of the pathologic process in our patient was indeed marked. Arnett and Roberts in their necropsy study of patients with active infective endocarditis found that the type or virulence of an organism did not play a significant role in the development of a ring abscess. In view of the clinical presentation of our patient and the findings at necropsy their report is of further interest. Aortic ring abscess occurred commonly and was also the most common cause of pericarditis in patients with active infective endocarditis. Only half of all their cases with pericarditis had clinical evidence of it. The aortic valve was the one almost exclusively affected by a ring abscess and if so always was accompanied by aortic valve regurgitation. Retrospectively our patient had four of the five features which according to them serve as clinical clues to the presence of a valve ring abscess: (1) pericarditis, (2) aortic valve involvement, (3) evidence of valvular regurgitation of recent origin and (4) recent origin and short duration of symptoms leading to severe debility or death. A V block was not present. It appears therefore that when a patient presents with a clinical picture of fulminant infection and has evidence of pericarditis the diagnosis of endocarditis with an aortic ring abscess should not be easily dismissed.

We conclude that (1) *Chlamydia trachomatis* must now be added to the list of organisms that may cause infective endocarditis with negative blood cultures, (2) *Chlamydia trachomatis* must be considered in addition to *Neisseria gonorrhoea* to be another venereal disease causing microorganism that is potentially capable of producing infective endocarditis of a normal heart valve, (3) the echocardiographic abnor-

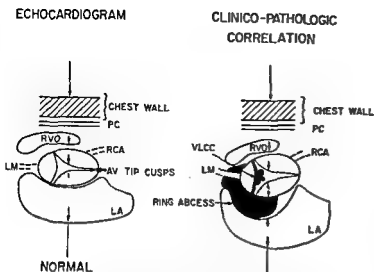


Fig 11 Vertical arrows indicate course of echobeam. On the left side is a diagram of the course of the echobeam through cardiac structures in the normal heart. On the right the diagram depicts the course of the echobeam through cardiac structures of our case. It explains why the aortic vegetation on the left coronary cusp was not visible on the echocardiogram because it was not located in the course of the echobeam. The (black) ring abscess on the other hand is located in the course of the beam and it explains the changes in the aortic wall visible in the echogram. Compare with Figs 4 and 6. AV = aortic valve, LA = left atrium, LM = left main coronary artery, PC = pericardium, RCA = right coronary artery, RVO = right ventricular outflow tract, VLCC = vegetation on left coronary cusp.

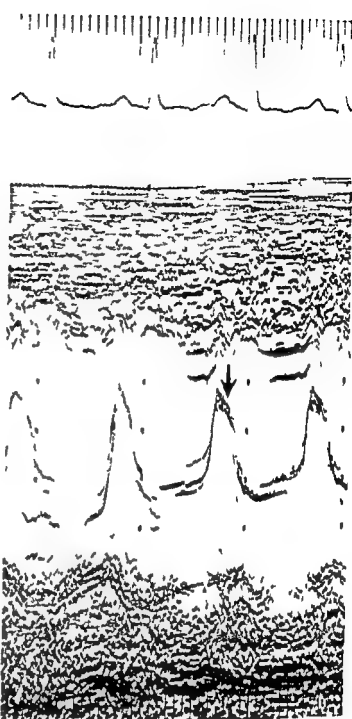


Fig 12 Portion of an echocardiographic sweep from the mitral valve to the aorta. As the transducer approaches the aorta increased echoes are seen from the anterior mitral leaflet (arrow).

underlying cardiac disease and there was no evidence of previous valvular disease. While the results of the serologic studies indicate evidence of an active infection with *Chlamydia trachomatis* type F (irrespective of site or source) and the ultrastructural findings in the valve vegetation reveal *Chlamydia* (irrespective of subtype) only the combination of the two substantiates in our case the diagnosis of *Chlamydia trachomatis* endocarditis.

collected on August 28 also contained IgM antibody extensively cross reacting with antigens of E O and L immunotypes. This cross reaction was rather unusual. It has been shown that IgM antibody may disappear within one month after acute chlamydial infection.<sup>7</sup> The stable IgG antibody titer of 1:64 to type J antigen but no IgM antibody probably indicates that the patient had previous *Chlamydia trachomatis* type J infections. It is also known that antibody to type J antigen cross reacts with type C antigen.<sup>8</sup> Our patient had a history of vaginal discharge early during her pregnancy. Although no definitive diagnosis was made, it is very tempting to speculate that it might have been due to *Chlamydia trachomatis* type J genital infection.

*Chlamydia trachomatis* causes both ocular and genital diseases in humans.<sup>9</sup> There was no evidence of eye disease in our patient. However, she did have vaginal discharge. Although the cervical discharge was not cultured for chlamydia, it is most likely that she had genital *Chlamydia trachomatis* infection. It is not clear why she had hematogenous dissemination leading to infection of the aortic valve. She had no apparent

# Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia Report of a patient with normal coronary arteriograms

Kamal K Chawla MD FACC FRCP (C)\*  
 Jairo Cruz MD\*  
 Neil E Kramer MD FACC\*  
 William D Towne MD FACC FACP FCCP\*\*\*\*  
 Chicago Ill

Electrophysiological effects of moderate to severe hyperkalemia and its effect on the electrocardiogram have been well described by various authors. Shortening of QT interval tenting of T waves lengthening of PR interval loss of P wave causing sinoventricular rhythm and finally broadening of QRS and sine wave are some of the more commonly described abnormalities. ST segment changes resembling a current of injury have been rarely reported. However in none of the previously reported cases was coronary artery disease ruled out with any certainty.

We observed a patient with diabetic ketoacidosis and hyperkalemia who showed marked ST segment elevations resembling acute anterior wall myocardial infarction. Treatment of hyperkalemia resulted in prompt return of the ECG towards normal. Subsequent work up including exercise testing and selective coronary arteriography ruled out any significant coronary artery

disease suggesting that the ECG changes were probably caused by hyperkalemia.

## Case report

G C a 48-year old black male was admitted to Cook County Hospital because of diabetic ketoacidosis. The patient was a known diabetic for the last 10 years controlled with 40 units of NPH insulin. Two weeks prior to admission he had developed mild fever and a non-productive cough. He had also noted fatigue weakness, and dyspnea on moderate exertion. He also complained of nausea and had vomited a few times. The patient denied any history of chest pain. In the past he had been treated for pulmonary tuberculosis. There was no history of hypertension. The patient had smoked 20 to 40 cigarettes a day for about 30 years.

On examination the patient was a moderately built although somewhat undernourished black male in mild respiratory distress. He was drowsy but well oriented. The heart rate was 100 beats/minute blood pressure 150/80 mm Hg temperature 99 F and respiratory rate 28/minute. The skin was dry and neck veins were flat. CVP measured 10 cm of H<sub>2</sub>O. The lungs showed slightly decreased breath sounds in right upper zone. Examination of the heart was entirely normal. Specifically no S<sub>4</sub> or friction rub was heard by any examiner.

Initial laboratory data showed marked hyperkalemia, acidosis, hyperglycemia and ketonemia compatible with the picture of severe diabetic ketoacidosis (see Table 1). The ECG on admission showed marked ST segment elevation in Leads V<sub>1</sub>, V<sub>2</sub> and aVL suggestive of acute anterior wall injury. There were also tall peaked T waves in the Leads V<sub>1</sub> through V<sub>4</sub> compatible with hyperkalemia (see Fig 1 upper panel). With the presumptive diagnosis of acute myocardial infarction the patient was transferred to the ICCU where close monitoring and tardant treatment of acute diabetic ketoacidosis consisting of regular insulin sodium bicarbonate and fluid replacement was instituted. Serial ECGs and enzymes determinations were obtained. Over the next 24 to 48 hours the patient showed marked improvement in his general condition as well as in the biochemical data. His blood sugar came down

From the Div of Adult Cardiology Cook County Hospital Chicago Ill.

Received for publication May 23, 1977.

Accepted for publication July 1, 1977.

Reprint requests: Kamal K Chawla MD Director of Adult Cardiology Cook County Hospital, Chicago Ill 60612.

Attending Physician Division of Adult Cardiology and Director of Electrocardiography and Human Physiology Laboratory Cook County Hospital, Chicago Ill.

Fellow Division of Adult Cardiology Cook County Hospital, Chicago Ill.

Attending Physician Division of Adult Cardiology and Director of Laboratory Cook County Hospital, Chicago Ill.

Chairman, Division of Adult Cardiology Cook County Hospital, Chicago Ill.



malty herein described must be added to the list of manifestations of bacterial endocarditis and also to the differential diagnosis of apparent abnormal widening of the posterior aortic wall

# Summary

A case of infective endocarditis due to *Chlamydia trachomatis* immunotype F is reported. Multiple negative blood cultures were a major deterrent from the initial clinical diagnosis of infective endocarditis. Postmortem ultrastructural identification of *Chlamydia* in the aortic valve vegetation led to an intensive retrospective study of retrieved serum samples utilizing microimmunofluorescent tests. Likewise an unusual echocardiographic finding was discovered to be the ultrasonic visualization of an aortic ring abscess. No similar case could be found in the literature.

Chnopathologic correlations are presented.

We are most indebted to Professor San pin Wang, Department of Pathobiology, School of Public Health and Community Medicine, University of Washington, and Dr Willy Burdorff, Head of the Rickettsial Diseases Section, Rocky Mountain Laboratory, for their assistance in performing the serologic studies. We thank Dr J. Alspaugh and Dr Calvin C. Linnemann, Jr. for their interest and assistance. We also thank Mrs. Jan Kluesener for typing the manuscript and Mr. Paul H. Glass for the excellent photographs.

# REFERENCES

1. Watanakunakorn C. Changing epidemiology and newer aspects of infective endocarditis. *Adv Intern Med* 22:21, 1977.
2. Kristinson A and Bentall H H. Medical and surgical treatment of Q fever endocarditis. *Lancet* 2:693, 1967.
3. Wilson H G, Neilson G H, Galea E G, Stafford G and O'Brien M F. Q fever endocarditis in Queensland. *Circulation* 53:680, 1976.
4. Levinson D A, Guthrie W, Ward C and Green D M. Infective endocarditis as part of psittacosis. *Lancet* 2:844, 1971.
5. Wang J P and Grayston J T. Human serology in *Chlamydia trachomatis* infection with microimmunofluorescence. *J Infect Dis* 130:388, 1974.
6. Moulder J W. The relation of the psittacosis group (Chlamydiae) to bacteria and viruses. *Ann Rev Microbiol* 20:107, 1966.
7. Schaffner W, Drutz D J, Duncan G W and Koenig M G. The clinical spectrum of endemic psittacosis. *Arch Intern Med* 119:433, 1967.
8. Grayston J T and Wang S P. New knowledge of chlamydiae and the diseases they cause. *J Infect Dis* 132:87, 1975.
9. Richmond S J and Sparling P F. Genital chlamydial infections. *Am J Epidemiol* 103:428, 1976.
10. Beem M O and Saxon E M. Respiratory tract colonization and a distinctive pneumonia syndrome in infants with *Chlamydia trachomatis*. *N Eng J Med* 296:306, 1977.
11. Higashi N. Electron microscopic studies on the mode of reproduction of Trachoma virus and Psittacosis virus in cell cultures. *Exp Mol Pathol* 4:24, 1965.
12. Storz J and Page L A. Taxonomy of Chlamydiae. Reasons for classifying organisms of the genus *Chlamydia* as family Chlamydiaceae in a separate order Chlamydiales ord nov. *Int J Syst Bacteriol* 21:332, 1971.
13. Armstrong J A and Reed M. Nature and origin of initial bodies in lymphogranuloma venereum. *Nature* 201:371, 1964.
14. Eb F, Orfila J and Lefebvre J F. Ultrastructural study of the development of the agent of Ewe's abortion. *J Ultrastructure* 56:177, 1976.
15. Eb F, Devauchelle G and Orfila J. Étude ultrastructurale de l'agent de la lymphogranulomatose vénérienne (rickettsiales: Chlamydiaceae). *J Microscopie* 13:47, 1972.
16. Schachter J. Chlamydiae, chapter 67. *Manual of clinical microbiology*. Rose N R and Friedman H ed. Washington D C 1976. American Society for Microbiology.
17. Dillon J C, Feigenbaum H, Konecny L H, Davis R H and Chang S J. Echocardiographic manifestations of valvular vegetations. *Am Heart J* 86:698, 1973.
18. Martinez E C, Burch G E and Giles T D. Echocardiographic diagnosis of vegetative aortic bacterial endocarditis. *Am J Cardiol* 34:698, 1974.
19. Wray T. The variable echocardiographic features in aortic valve endocarditis. *Circulation* 52:688, 1975.
20. Hirschfeld D J and Schiller N. Localization of aortic valve vegetations by echocardiography. *Circulation* 53:280, 1976.
21. Pierre R, Tajik A J, Guliani E R et al. Spectrum of echocardiographic findings in bacterial endocarditis. *Circulation* 53:474, 1976.
22. Nanda N C, Gramiak R and Shah P M. Diagnosis of aortic root dissection by echocardiography. *Circulation* 58:506, 1973.
23. Moothart R W, Spangler R D and Blount S G. Echocardiography in aortic root dissection and dilatation. *Am J Cardiol* 36:11, 1975.
24. Brown O R, Popp R and Kloster F E. Echocardiographic criteria for aortic root dissection. *Am J Cardiol* 36:17, 1975.
25. Arnett E N and Roberts W C. Valve ring abscess in active infective endocarditis. *Circulation* 54:140, 1976.
26. Holmes K K, Counts G W and Beaty H N. Disseminated gonococcal infection. *Ann Intern Med* 74:979, 1971.



Fig 2 Coronary arteriograms A Left coronary artery in the left anterior oblique (60 degree) projection and B right coronary artery in the left anterior oblique (40 degree) projection showing all branches widely patent

Table I Laboratory data

|   | Date     | Time      | Serum<br>K<br>(mEq/L) | pH   | Serum<br>glucose<br>(mgm %) | S<br>bicarb<br>(mEq/L) | ECG                                       |
|---|----------|-----------|-----------------------|------|-----------------------------|------------------------|---|
| A | 11/8/76  | 1 20 A.M. | 6.3                   | 7.09 | 640                         | 6.8                    | Injury pattern and tented T waves         |
| B | 11/8/76  | 7 10 A.M. | 4.3                   | 7.35 | 348                         | 14.1                   | Slight ST elevation and tented<br>T waves |
| C | 11/10/76 | 7 00 A.M. | 4.0                   | 7.44 | 457                         | 25.6                   | Normal                                    |

The hyperkalemia of ketoacidosis differs from that of other causes in that there is a shift of potassium out of the cell resulting in an altered ratio of intracellular to extracellular potassium.<sup>1,2</sup> This may contribute in part to the severity of the ST segment elevations in the setting of diabetic ketoacidosis. It is also possible that the associated severe acidosis and marked hyperglycemia present in our patient may have added to the effect of hyperkalemia in producing the observed ECG changes.

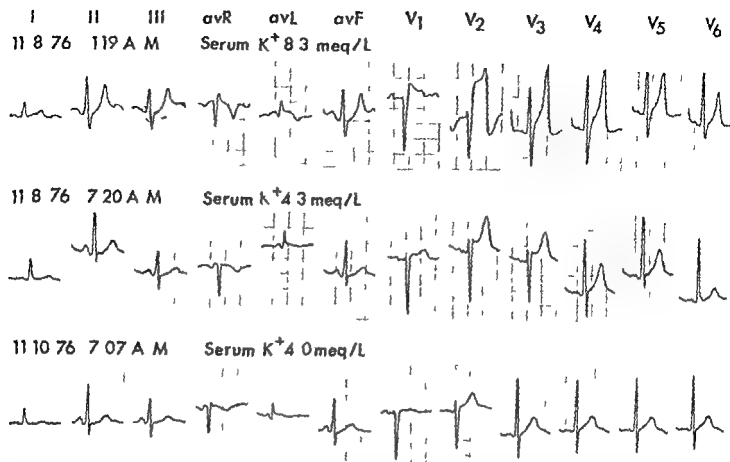
Electrocardiographic abnormalities resembling myocardial infarction in the presence of severe hyperkalemia have been reported by several observers in the past.<sup>3-5</sup> Pathological Q waves as well as ST-T changes resembling acute injury pattern have been described separately. The appearance of pathological Q waves has generally been attributed to altered initial QRS forces secondary to intraventricular conduction abnormalities resulting from hyperkalemia.<sup>6</sup>

Levine and associates<sup>7</sup> reported four cases of acute renal failure with hyperkalemia and ST-T patterns suggesting myocardial infarction. In all

of these patients lowering of the serum potassium level by hemodialysis was associated with return of the electrocardiogram towards normal. However in two of the four patients fibrous pericarditis was noted to be present at autopsy and this may have had an effect on the ECG of these two patients. In the third patient a left bundle branch block pattern was present which of course renders the ECG diagnosis of acute myocardial infarction difficult. The fourth patient was not autopsied so that neither coronary artery disease nor pericarditis both of which can be associated with renal failure were ruled out.

Gelzayd and Holzman<sup>8</sup> reported a case of diabetic ketoacidosis with hyperkalemia presenting with ECG abnormalities similar to that of our patient. However neither coronary arteriography nor exercise testing was reported as performed in their patient.

Lichstein and colleagues<sup>9</sup> reported two patients with hyperkalemia induced fascicular block one of whom had marked ST segment elevation in Leads V<sub>1</sub> and V<sub>2</sub> similar to those of our patient. The resemblance of the ST-T changes to those of



**Fig 1** Serial electrocardiograms. The top panel represents a twelve lead ECG on admission showing marked ST segment elevations in Leads V<sub>1</sub>, V<sub>2</sub> and aVL. Middle panel shows same twelve leads six hours later when the serum potassium has come down to 4.3 mEq/L. Notice the marked improvement in the ST segment elevation and T wave abnormality. Lower panel recorded two days later shows normal ECG when serum K<sup>+</sup> is 4.0 mEq/L.

from 840 to 452 mg per cent. The serum K<sup>+</sup> came down from 8.3 to 4.0 mEq/L and the pH increased from 7.09 to 7.44 (see Table 1). The electrocardiogram taken six hours after admission when the serum K<sup>+</sup> had come down to 4.3 mEq/L showed marked decrease in the ST segment elevation. However slight J point and early ST segment elevation and some T wave tenting persisted (Fig 1 middle panel). Subsequent ECGs two and three days later were completely within normal limits (Fig 1 lower panel). Slight QRS prolongation which had been noted on the admission ECG was absent in subsequent tracings. The frontal plane QRS axis remained unchanged throughout the patient's course. The cardiac enzymes remained grossly within normal limits. The patient made an uneventful recovery and was placed back on NPH insulin.

Ten days later a treadmill exercise test was performed using the Bruce protocol. The patient reached the predicted level of 6 to 7 mets and a maximal heart rate of 150 beats/minute (87 per cent of maximum predicted for the age). The ECG did not show abnormal ST segment changes or arrhythmia and the patient did not complain of chest pain. The test was considered negative for ischemic response.

Cardiac catheterization was performed two weeks after the admission and selective coronary arteriograms were obtained in multiple views. Both the left and right coronary arteries and their major branches were visualized and appeared completely free of any obstructive lesions (Fig 2). Left

ventricular function was also normal with an ejection fraction of 69 per cent.

## Discussion

Increased plasma potassium may occur spontaneously or iatrogenically. Some of the more frequent clinical causes include renal failure, untreated diabetic ketoacidosis, adrenocortical insufficiency, and over enthusiastic therapeutic use of potassium salts or drugs with high potassium content.

An increase in the concentration of extracellular potassium lowers the resting membrane potential leading to a reduction of the upstroke velocity, amplitude and duration of the action potential. This effect has been recorded in atrial, ventricular and Purkinje fibers and may be manifested on the ECG by changes in the amplitude and duration of the P wave and QRS complex.<sup>1-4</sup> The mechanism of T wave and ST segment changes is not well understood and has not been well correlated with action potential abnormalities.

## Low renin ( primary ) hyperaldosteronism

### Differential Diagnosis and Distinction of Sub-Groups Within The Syndrome

J H Ferriss  
D G Beevers  
J J Brown  
R Fraser  
A E Lever  
P I Padfield  
J I S Robertson  
Glasgow Scotland

In an earlier paper we discussed the clinical biochemical and pathological features of low renin hyperaldosteronism (primary hyperaldosteronism). This review is concerned with the differential diagnosis of the condition and a third paper describes treatment.

Primary hyperaldosteronism is usually associated either with a unilateral adrenocortical adenoma or with bilateral hyperplasia of the zona glomerulosa rarely the syndrome may be associated with an adrenal or other carcinoma and very occasionally the abnormalities are reversible by glucocorticoids. To facilitate treatment these several forms must be differentiated one from another.

As a group however such patients must first be distinguished from those suffering from other varieties of hypertension with mineralocorticoid excess and from those cases of apparently essential hypertension with renin suppression. A classification of hypertension associated with mineralocorticoid excess is shown in Table I. Part I of this paper describes the differential diagnosis of primary hyperaldosteronism; part II describes the distinction of the various forms within the syndrome.

### Part I The differential diagnosis of primary hyperaldosteronism

Conditions with which primary hyperaldosteronism may be confused are outlined in Table I.

**Secondary hyperaldosteronism** Primary and secondary hyperaldosteronism can be differentiated by measurements of renin and angiotensin II in plasma. In the latter aldosterone excess results from increased circulating levels of renin and its active product angiotensin II which in turn result usually from sodium depletion or renal disease.<sup>1</sup> By contrast primary hyperaldosteronism is associated with inappropriately low circulating levels of renin and angiotensin II.<sup>2</sup> Even without such measurements plasma sodium serves as a rough guide to renin levels as plasma renin concentration and plasma sodium are inversely correlated in hypertension.<sup>3</sup> Thus in a patient with hypertension and hypokalemia in whom aldosterone excess is shown or suspected, hyponatremia points to a cause associated with high renin levels while a high plasma sodium suggests primary hyperaldosteronism.

The common causes of secondary hyperaldosteronism with hypertension are outlined below (see Table I).

**Hyperaldosteronism due to diuretic therapy** This is probably the most frequent cause of aldosterone excess in hypertensive patients. Diuretic induced sodium loss leads to a secondary elevation of renin, angiotensin II and aldosterone.<sup>4</sup> Its importance is that it may mimic or obscure other causes of hyperaldosteronism. If

From the Medical Research Council Blood Pressure Unit and the University Department of Medicine, Western Infirmary, Glasgow, Scotland.

Received for publication May 11 1976.

Reprint requests: Dr J I S Robertson, MRC Blood Pressure Unit, Western Infirmary, Glasgow G4 7NT, Scotland.

acute antero-septal myocardial infarction is evident from their Fig 1 although the authors do not call attention to this point. The pattern is described as showing right bundle branch block and left anterior hemiblock. However, these conduction abnormalities, unlike left bundle branch block, do not by themselves explain the observed ST-T changes.

The findings in our patient reemphasize the previously reported observation that hyperkalemia may produce marked ST-T changes resembling those of acute myocardial infarction. To the best of our knowledge, there is no previous report in the literature of a patient with the hyperkalemia-induced ECG changes of acute myocardial infarction in whom coronary artery disease was judged unlikely on the basis of negative exercise electrocardiography or ruled out by normal selective coronary arteriograms. We would conclude that hyperkalemia should be considered in the differential diagnosis of ST-T changes resembling acute myocardial infarction, especially when these occur in those clinical settings where hyperkalemia is frequently observed.

### Summary

A patient is described with severe diabetic ketoacidosis and hyperkalemia who presented with an ECG resembling an acute anterior wall myocardial infarction. Treatment of hyperkalemia resulted in prompt return of the ECG towards normal. Subsequent work-up including exercise testing and selective coronary arteriography ruled out any significant coronary artery

disease suggesting that the ECG changes were probably caused by hyperkalemia. While similar changes have rarely been described in the past, this would appear to be the first such case in whom coronary artery disease was ruled out by a negative exercise testing and coronary arteriography.

We thank Miss Suzanne Adams for her expert secretarial assistance.

### REFERENCES

1. Littinger P O, Regan T J and Oldewurtel H A. Hyperkalemia, cardiac conduction and the electrocardiogram. A review. *Am Heart J* 88:360, 1974.
2. Gelzayd E A and Holzman D. Electrocardiographic changes of hyperkalemia simulating acute myocardial infarction. Report of a case. *Dis Chest* 51:211, 1967.
3. Arnsdorf M F. Electrocardiogram in hyperkalemia. Electrocardiographic pattern of antero-septal myocardial infarction mimicked by hyperkalemia-induced disturbance of impulse conduction. *Arch Intern Med* 136:1161, 1976.
4. Lichstein E, Gupta P K and Grumwald A A. Hyperkalemic fascicular block. Electrocardiogram of the month. *Chest* 70:290, 1976.
5. Levine H D, Wanzer S H and Merrill J P. Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis. *Circulation* 13:29, 1956.
6. Fisch C, Knoebel S B, Feigenbaum H and Green span K. Potassium and the monophasic action potential. Electrocardiogram conduction and arrhythmias. *Progr Cardiovasc Dis* 8:387, 1966.
7. Cohen H C, Rosen K M and Pick A. Disorders of impulse conduction and impulse formation caused by hyperkalemia in man. Case report. *Am Heart J* 89:501, 1975.
8. Nadler C M, Bellet S and Lanning M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am J Med* 5:839, 1948.

terone point to a renal rather than an adrenal abnormality. The diagnosis is confirmed by demonstrating higher concentrations of renin and angiotensin in the renal vein of the affected side compared with the opposite in the absence of renal artery stenosis and by the radiological appearances on selective renal arteriography. The lesion is usually a benign juxta glomerular cell tumor rich in renin. Removal of the affected kidney will reverse both the hypertension and the biochemical abnormalities.

**Congenital hyperaldosteronism.** Prior to the era of renin assays a number of children and young adults were described with hypertension and hyperaldosteronism in whom total or sub total adrenalectomy often resulted in a marked blood pressure fall. Adrenocortical adenomas were not found and the glands showed either adrenocortical hyperplasia or normal histology.<sup>20</sup> Several had symptoms dating back to infancy or early childhood and some were mentally or physically retarded. The term congenital aldosteronism has been applied to this group.<sup>20</sup> In the absence of renin measurements it is difficult to exclude the possibility that hyperaldosteronism was secondary to unrecognized renal disease to malignant hypertension (which was present in some)<sup>21</sup> or even to a renin secreting renal tumor. However such causes seem less likely in those who showed a sustained blood pressure fall after adrenalectomy.

**Hypertensive disease of pregnancy.** Normal pregnancy is associated with marked increases in plasma concentrations of renin, renin substrate, angiotensin II and aldosterone, although in contrast to the non pregnant state there is not a close correlation between these variables. In women with hypertension and proteinuria in late pregnancy, renin, angiotensin II and aldosterone levels are suppressed although apart from angiotensin II often still above the normal non pregnant range. This suggests that the renin-angiotensin-aldosterone system does not play a direct pathogenic role in hypertension of pregnancy although Gordon and associates<sup>22</sup> proposed that increases in the renin-angiotensin-aldosterone system appropriate to normal pregnancy may aggravate established pre-eclampsia by failing to decline in late pregnancy.

**Hypertension and the oral contraceptive.** A small but definite rise in blood pressure occurs in most women taking estrogen/progestogen oral

contraceptives<sup>23</sup> and rarely severe hypertension may occur. The mechanism for this blood pressure increase is uncertain. Oral contraceptives produce an increase in plasma renin substrate and a fall in plasma renin concentration<sup>24</sup> with a variable change in plasma angiotensin II. Plasma aldosterone is not consistently increased<sup>25</sup> and Weir and colleagues<sup>26</sup> were unable to show a correlation between blood pressure and concurrent plasma measurements of renin, renin substrate, angiotensin II, aldosterone, cortisol or DOC nor was angiotensin II disproportionately high in relation to exchangeable sodium. As yet there is no convincing evidence that changes in the renin-angiotensin-aldosterone system are responsible for the blood pressure rise induced by oral contraceptives.

**Hypertension with excess of a mineralocorticoid other than aldosterone.**

**11 Deoxycorticosterone.** Brown and associates described persistently elevated plasma deoxycorticosterone (DOC) levels in six of 21 patients with hypertension, low plasma renin and normal plasma aldosterone and 11 hydroxycorticosteroids. Hypokalemia was observed in five. Odde and colleagues<sup>27</sup> reported moderately raised plasma DOC concentrations in three of 14 patients with essential hypertension. Cope and Loizou<sup>28</sup> reported increased DOC excretion in five of seven patients with hypertension and hypokalemia although aldosterone excretion was also increased in one and another had a pancreatic carcinoma with an associated ectopic ACTH syndrome. Others have reported normal secretion rates or plasma levels of DOC in essential hypertension.

Hypertension with DOC excess has also been reported in association with an adrenocortical carcinoma.<sup>29</sup>

**18 hydroxydeoxycorticosterone.** Melby and co-workers<sup>30</sup> reported increased secretion of 18 hydroxydeoxycorticosterone (18 OH DOC) in three of 12 patients with hypertension and suppressed plasma renin activity. Aldosterone secretion was normal or low and DOC excretion was also low. 18 OH DOC excretion was normal in each of 17 hypertensive patients with normal plasma renin activity. Similarly, Genest and Nowaczynski<sup>31</sup> reported increased 18 OH DOC secretion in some patients with essential hypertension.

**Corticosterone.** We are aware of one report of

**Table 1** Classification of hypertension associated with mineralocorticoid excess

- 1 *Aldosterone excess with low plasma renin (primary hyperaldosteronism)*
  - a Adrenocortical adenoma
  - b Hyperplasia of the zona glomerulosa with micronodules (including a sub group with normal adrenal appearance)
  - c Glucocorticoid remedial hyperaldosteronism
  - d Adrenocortical carcinoma
  - e Hyperaldosteronism associated with ovarian tumors
- 2 *Aldosterone excess with high plasma renin (secondary hyperaldosteronism)*
  - a Benzothiadiazine diuretics
  - b Renal artery stenosis and unilateral renal diseases
  - c Malignant phase hypertension
  - d Chronic bilateral renal disease
  - e Renin secreting renal tumor
  - f Congenital hyperaldosteronism
  - g Hypertensive disease of pregnancy
- 3 *Non aldosterone mineralocorticoid excess*
  - a Deoxycorticosterone
  - b 18 hydroxy deoxycorticosterone
  - c Corticosterone
  - d 16  $\beta$  hydroxy dehydroepiandrosterone
  - e Abnormalities of corticosteroid synthesis
  - f Cushing syndrome
  - g Lacosone and carbenoxolone induced hypertension
- 4 *Low renin essential hypertension*  
(mineralocorticoid excess unproved—see text)

another cause is suspected diuretic treatment should be stopped and the patient then reassessed. In view of the findings of Relman,<sup>5</sup> diuretics should be omitted for at least three weeks before investigation.

**Hyperaldosteronism with renal artery stenosis**  
Many cases of renal artery stenosis especially those with malignant phase hypertension, are associated with elevated levels of renin, angiotensin II and aldosterone.<sup>1-10</sup> It has been postulated that the affected kidney receives an inappropriate signal for renin release.<sup>1</sup> The resultant high levels of angiotensin II stimulate aldosterone secretion favoring sodium retention. However the raised arterial pressure provokes a natriuresis from the unaffected kidney and the increased levels of angiotensin II may cause further sodium loss from both the post stenotic and unaffected sides.<sup>11</sup> Total exchangeable and serum sodium may be reduced.<sup>12</sup> Surgical relief of the stenosis often corrects both the hypertension and the biochemical abnormalities.<sup>3,4</sup>

#### *Hyperaldosteronism with malignant phase hy-*

*pertension* Malignant phase hypertension in the absence of a demonstrable renal or renovascular lesion is also often associated with high circulating levels of renin, angiotensin II and aldosterone.<sup>3,4,10,11,13</sup> It may be that intrarenal arterial or arteriolar lesions resulting from malignant phase hypertension produce an effect on renin secretion similar to that found in renal artery stenosis, certainly plasma angiotensin II levels are usually high in relation to total exchangeable sodium.<sup>14</sup> Adequate control of the hypertension permits those lesions to heal and the elevated levels of renin, angiotensin, and aldosterone may then revert to normal.<sup>11,15</sup>

Increased angiotensin II levels as such are unlikely to produce the malignant phase. Plasma angiotensin II is sometimes normal,<sup>16</sup> malignant hypertension can occur in the rat when renin is subnormal<sup>17</sup> and indeed in man low renin hyperaldosteronism may be associated with malignant phase hypertension.<sup>4</sup>

**Hyperaldosteronism in chronic renal failure**  
In the majority of patients undergoing regular hemodialysis for chronic renal failure blood pressure is controlled by removing sodium and water at dialysis and by restricting sodium and water intake between dialyses. In a minority these measures are ineffective and severe intractable hypertension develops associated with high levels of renin, angiotensin II and aldosterone.<sup>12,18</sup> Removal of sodium and water at dialysis fails to control the blood pressure and results in yet higher levels of renin and angiotensin, disproportionately high in relation to exchangeable sodium.<sup>19</sup> It may be that in this minority the grossly diseased kidneys provide an inappropriate signal for renin release. Bilateral nephrectomy is followed by a rapid fall in renin and angiotensin levels and blood pressure thereafter is usually readily controlled.<sup>20</sup> Further evidence of the direct role of the renin-angiotensin system in maintaining hypertension in these patients is illustrated by the prompt and sustained fall of blood pressure produced during infusion of the angiotensin II antagonist saralasin.<sup>21,22</sup>

**Hypertension with a renin secreting renal tumor**  
A number of cases of hypertension and secondary hyperaldosteronism associated with renin secreting renal tumors have now been described.<sup>23</sup> Patients usually present with severe hypertension and hypokalemia. High circulating levels of renin, angiotensin and ald-

terone point to a renal rather than an adrenal abnormality. The diagnosis is confirmed by demonstrating higher concentrations of renin and angiotensin in the renal vein of the affected side compared with the opposite in the absence of renal artery stenosis and by the radiological appearances on selective renal arteriography. The lesion is usually a benign juxta glomerular cell tumor rich in renin removal of the affected kidney will reverse both the hypertension and the biochemical abnormalities.

**Congenital hyperaldosteronism.** Prior to the era of renin assays a number of children and young adults were described with hypertension and hyperaldosteronism in whom total or subtotal adrenalectomy often resulted in a marked blood pressure fall. Adrenocortical adenomas were not found and the glands showed either adrenocortical hyperplasia<sup>58</sup> or normal histology.<sup>59</sup> Several had symptoms dating back to infancy or early childhood and some were mentally or physically retarded the term congenital aldosteronism has been applied to this group.<sup>60</sup> In the absence of renin measurements it is difficult to exclude the possibility that hyperaldosteronism was secondary to unrecognized renal disease to malignant hypertension (which was present in some) or even to a renin-secreting renal tumor. However such causes seem less likely in those who showed a sustained blood pressure fall after adrenalectomy.

**Hypertensive disease of pregnancy.** Normal pregnancy is associated with marked increases in plasma concentrations of renin, renin substrate, angiotensin II and aldosterone although in contrast to the non pregnant state there is not a close correlation between these variables. In women with hypertension and proteinuria in late pregnancy renin, angiotensin II and aldosterone levels are suppressed although apart from angiotensin II often still above the normal non pregnant range. This suggests that the renin-angiotensin-aldosterone system does not play a direct pathogenic role in hypertension of pregnancy although Gordon and associates proposed that increases in the renin-angiotensin-aldosterone system appropriate to normal pregnancy may aggravate established pre-eclampsia by failing to decline in late pregnancy.

**Hypertension and the oral contraceptive.** A small but definite rise in blood pressure occurs in most women taking estrogen/progestogen oral

contraceptives<sup>61</sup> and rarely severe hypertension may occur. The mechanism for this blood pressure increase is uncertain. Oral contraceptives produce an increase in plasma renin substrate and a fall in plasma renin concentration<sup>62</sup> with a variable change in plasma angiotensin II.<sup>63</sup> Plasma aldosterone is not consistently increased<sup>64</sup> and Weir and colleagues<sup>65</sup> were unable to show a correlation between blood pressure and concurrent plasma measurements of renin, renin substrate, angiotensin II, aldosterone, cortisol or DOC nor was angiotensin II disproportionately high in relation to exchangeable sodium. As yet there is no convincing evidence that changes in the renin-angiotensin-aldosterone system are responsible for the blood pressure rise induced by oral contraceptives.

**Hypertension with excess of a mineralocorticoid other than aldosterone.**

**11 Deoxycorticosterone.** Brown and associates<sup>66</sup> described persistently elevated plasma deoxycorticosterone (DOC) levels in six of 21 patients with hypertension, low plasma renin and normal plasma aldosterone and 11 hydroxycorticosteroids. Hypokalemia was observed in five. Oddie and colleagues<sup>67</sup> reported moderately raised plasma DOC concentrations in three of 14 patients with essential hypertension. Cope and Loizou<sup>68</sup> reported increased DOC excretion in five of seven patients with hypertension and hypokalemia although aldosterone excretion was also increased in one and another had a pancreatic carcinoma with an associated ectopic ACTH syndrome. Others have reported normal secretion rates or plasma levels of DOC in essential hypertension.

Hypertension with DOC excess has also been reported in association with an adrenocortical carcinoma.<sup>69</sup>

**18 Hydroxydeoxycorticosterone.** Melby and co-workers<sup>70</sup> reported increased secretion of 18 hydroxydeoxycorticosterone (18 OH DOC) in three of 12 patients with hypertension and suppressed plasma renin activity. Aldosterone secretion was normal or low and DOC excretion was also low. 18 OH DOC excretion was normal in each of 17 hypertensive patients with normal plasma renin activity. Similarly Genest and Nowaczynski<sup>71</sup> reported increased 18 OH DOC secretion in some patients with essential hypertension.

**Corticosterone.** We are aware of one report of



**Table 1** Classification of hypertension associated with mineralocorticoid excess

- 1 Aldosterone excess with low plasma renin (primary hyperaldosteronism)
  - a Adrenocortical adenoma
  - b Hyperplasia of the zona glomerulosa with micronodules (including a sub group with normal adrenal appearance)
  - c Glucocorticoid remedial hyperaldosteronism
  - d Adrenocortical carcinoma
  - e Hyperaldosteronism associated with ovarian tumors
- 2 Aldosterone excess with high plasma renin (secondary hyperaldosteronism)
  - a Benzothiadiazine diuretics
  - b Renal artery stenosis and unilateral renal diseases
  - c Malignant phase hypertension
  - d Chronic bilateral renal disease
  - e Renin secreting renal tumor
  - f Congenital hyperaldosteronism
  - g Hypertensive disease of pregnancy
- 3 Non aldosterone mineralocorticoid excess
  - a Deoxycorticosterone
  - b 18 hydroxy deoxycorticosterone
  - c Corticosterone
  - d 16  $\beta$  hydroxy dehydroandrosterone
  - e Abnormalities of corticosteroid synthesis
  - f Cushing's syndrome
  - g Licorice and carbenoxolone induced hypertension
- 4 Low renin essential hypertension  
(mineralocorticoid excess unproved—see text)

another cause is suspected, diuretic treatment should be stopped and the patient then reassessed. In view of the findings of Rulman,<sup>1</sup> diuretics should be omitted for at least three weeks before investigation.

**Hyperaldosteronism with renal artery stenosis**  
Many cases of renal artery stenosis especially those with malignant phase hypertension are associated with elevated levels of renin, angiotensin II and aldosterone.<sup>1,2,10</sup> It has been postulated that the affected kidney receives an inappropriate signal for renin release. The resultant high levels of angiotensin II stimulate aldosterone secretion favoring sodium retention. However the raised arterial pressure provokes a natriuresis from the unaffected kidney and the increased levels of angiotensin II may cause further sodium loss from both the post stenotic and unaffected sides.<sup>11</sup> Total exchangeable and serum sodium may be reduced.<sup>12</sup> Surgical relief of the stenosis often corrects both the hypertension and the biochemical abnormalities.<sup>3,4</sup>

**Hyperaldosteronism with malignant phase hy**

**per-tension** Malignant phase hypertension in the absence of a demonstrable renal or renovascular lesion, is also often associated with high circulating levels of renin, angiotensin II and aldosterone.<sup>1,4,13,14</sup> It may be that intrarenal arterial or arteriolar lesions resulting from malignant phase hypertension produce an effect on renin secretion similar to that found in renal artery stenosis certainly plasma angiotensin II levels are usually high in relation to total exchangeable sodium.<sup>15</sup> Adequate control of the hypertension permits those lesions to heal and the elevated levels of renin, angiotensin, and aldosterone may then revert to normal.<sup>1,16</sup>

Increased angiotensin II levels as such are unlikely to produce the malignant phase. Plasma angiotensin II is sometimes normal.<sup>17</sup> Malignant hypertension can occur in the rat when renin is sub normal<sup>18</sup> and indeed in man low renin hyperaldosteronism may be associated with malignant phase hypertension.<sup>1</sup>

**Hyperaldosteronism in chronic renal failure**  
In the majority of patients undergoing regular hemodialysis for chronic renal failure blood pressure is controlled by removing sodium and water at dialysis and by restricting sodium and water intake between dialyses. In a minority these measures are ineffective and severe intractable hypertension develops associated with high levels of renin, angiotensin II and aldosterone.<sup>1,19</sup> Removal of sodium and water at dialysis fails to control the blood pressure and results in yet higher levels of renin and angiotensin disproportionately high in relation to exchangeable sodium.<sup>1,20</sup> It may be that in this minority the grossly diseased kidneys provide an inappropriate signal for renin release. Bilateral nephrectomy is followed by a rapid fall in renin and angiotensin levels and blood pressure thereafter is usually readily controlled. Further evidence of the direct role of the renin-angiotensin system in maintaining hypertension in these patients is illustrated by the prompt and sustained fall of blood pressure produced during infusion of the angiotensin II antagonist saralasin.<sup>21,22</sup>

**Hypertension with a renin secreting renal tumor**  
A number of cases of hypertension and secondary hyperaldosteronism associated with renin secreting renal tumors have now been described.<sup>23</sup> Patients usually present with severe hypertension and hypokalemia. High circulating levels of renin, angiotensin and aldosterone

are plasma and extracellular fluid volumes.<sup>20</sup> Earlier reports of an increase in exchangeable sodium<sup>21</sup> and extracellular fluid volume<sup>1</sup> have been challenged.<sup>22</sup> Furthermore there is no evidence of a bimodal distribution of plasma concentrations of renin<sup>23</sup> or of angiotensin II<sup>24</sup> in essential hypertension suggesting that the low renin state forms a part of a continuum in hypertension rather than a distinct diagnostic entity.

In summary the hypothesis that mineralocorticoid excess is the cause of most or all cases of low renin hypertension is as yet unproved.<sup>25</sup> An alternative possibility is that plasma renin falls as a result of renal adaption to long term hypertension possibly because of increased renal vascular resistance with an increase in filtration fraction.<sup>26</sup> This hypothesis is supported by observations that plasma renin concentration is inversely related to age in patients with essential hypertension<sup>27</sup> and that the normal rise in plasma renin concentration following intravenous furosemide is suppressed in hypertensive patients both with normal renin and low renin levels.<sup>28</sup>

Grim<sup>4</sup> proposed that normal aldosterone levels are inappropriately high in relation to renin in such patients and suggested that low renin hypertension represents an early form of primary hyperaldosteronism. Adrenal abnormalities including adenomas have been described in some patients. However as stated total exchangeable sodium<sup>21</sup>, extracellular and plasma volumes are normal in this group and we have shown that plasma aldosterone is usually suppressed by sodium loading in contrast to primary hyperaldosteronism with or without adenoma.

#### Part II Primary hyperaldosteronism: Differentiation of sub groups within the syndrome

As discussed<sup>1</sup> hypertension with secondary hyperaldosteronism is distinguished from primary hyperaldosteronism by measurements of renin and angiotensin II in plasma. Furthermore both an excess of mineralocorticoid other than aldosterone and low renin essential hypertension are associated with normal (or low) aldosterone values. However when aldosterone excess is associated with low levels of renin and angiotensin II it remains necessary to distinguish the various forms of primary hyperaldosteronism (Table I) to facilitate rational treatment.

Rare causes such as glucocorticoid remediable hyperaldosteronism and aldosterone excess associated with an adrenocortical or ovarian carcinoma must be identified. However the main diagnostic problem is in differentiating the two more common forms: a unilateral adrenocortical adenoma and bilateral hyperplasia of the zona glomerulosa.

**Glucocorticoid remediable hyperaldosteronism** A number of patients have been described with hypertension, hypokalemia, hyperaldosteronism and low plasma renin in whom all the abnormalities were reversed by glucocorticoids.<sup>29-31</sup> Such cases may be familial<sup>32</sup> and adrenal exploration has revealed adrenocortical hyperplasia without tumor.<sup>33-35</sup> The cause of this abnormality remains unknown.<sup>36</sup> Dexamethasone in small dosage often reversed all abnormalities within two weeks<sup>37</sup> although longer periods of treatment may be required.<sup>38</sup>

Blood pressure and plasma electrolytes were unchanged in all of 19 patients in our series given dexamethasone for two weeks.<sup>39</sup> However a trial of glucocorticoid suppression seems mandatory in all patients with primary hyperaldosteronism especially those in whom a tumor is not identified.

**Hyperaldosteronism associated with an adrenocortical carcinoma or an ovarian tumor** Excessive aldosterone production by an adrenocortical carcinoma is a rare cause of primary hyperaldosteronism. Early recognition is important particularly when conservative management is being considered. Such cases usually show characteristic features to alert the physician:<sup>40</sup> Fever, severe muscle weakness and abdominal pain are common. An abdominal tumor may be palpable or displace a kidney on pyelography or arteriography. Excessive secretion of adrenocorticoids other than aldosterone may occur and increased urinary excretion of 17 oxogenic and/or 17 oxosteroids is usual although not invariably.<sup>41,42</sup>

Two patients with hyperaldosteronism associated with an ovarian tumor have been reported. The adrenal glands appeared normal in each but aldosterone was extracted from the tumor tissue. One was a 9 year old girl with precocious puberty in whom a Sertoli cell tumor was found. The other presented with a widely metastasizing arrhenoblastoma; plasma levels of 17 $\beta$  oestradiol and testosterone were also elevated.

apparently isolated corticosterone excess.<sup>61</sup> This patient presented with hypertension, hypernatremia, hypokalemia, and edema and an adrenal cortical carcinoma was found at operation. Plasma concentrations of aldosterone and cortisol were normal but plasma corticosterone was grossly raised. Plasma DOC was not measured.

**16 $\beta$  hydroxydehydroepiandrosterone (16 $\beta$  OH DHEA)** Recently raised levels of urinary 16 $\beta$  OH dehydroepiandrosterone were described in patients with low renin hypertension.<sup>62</sup> This steroid was reported to have mineralocorticoid activity which, in the rat, was blocked by spironolactone.<sup>63</sup> However, a recent report<sup>152</sup> has failed to confirm elevated plasma levels of this compound in low renin essential hypertension.

**Congenital abnormalities of corticosteroid synthesis** Hypertension associated with mineralocorticoid excess occurs with 17 $\alpha$  hydroxylase and 11 $\beta$  hydroxylase deficiencies, but is not usually a feature of the commoner 21 hydroxylase abnormality. The raised blood pressure in such patients can be lowered towards normal by treatment with dexamethasone.

**17 $\alpha$  hydroxylase deficiency** This usually presents with hypertension and hypokalemia which in females is associated with primary amenorrhea and in males with pseudohermaphroditism. It is associated with relative cortisol deficiency, excessive deoxycorticosterone and corticosterone due to high ACTH levels, hypoadosteronism and low plasma renin.<sup>64-66</sup> In a case recently studied by us,<sup>163, 164</sup> dexamethasone treatment suppressed the elevated ACTH and returned the enhanced levels of ACTH dependent mineralocorticoids to normal. Expanded exchangeable sodium fell and contracted exchangeable potassium expanded, while hypertension was relieved. Subnormal plasma renin, angiotensin II and aldosterone rose into their normal ranges.

**11 $\beta$  hydroxylase deficiency** This condition usually presents with hypertension and virilism. There is impaired formation of cortisol, corticosterone and aldosterone with deoxycorticosterone excess.<sup>71, 72</sup>

**Cushing's syndrome** Hypokalemic alkalosis may occur in Cushing's syndrome of various aetiologies.<sup>73-74</sup> While plasma renin is occasionally suppressed,<sup>74-75</sup> aldosterone production is usually normal or decreased.<sup>73, 76, 77, 153</sup> Christy and Laragh<sup>74</sup> reported that plasma cortisol is signifi-

cantly higher in those with hypokalemia compared with normokalemic patients and postulated that the hypokalemic alkalosis is caused by higher cortisol secretion rates. However, in addition to the cortisol excess, increased production and plasma levels of corticosterone and deoxycorticosterone may occur, especially associated with adrenal carcinoma or an ectopic source of ACTH.<sup>54, 57, 60, 88</sup>

**Licorice and carbenoxolone induced hypertension** Licorice contains glycyrrhizic acid which has a mineralocorticoid effect. Consumption of large quantities of licorice containing substances may lead to hypertension, sodium retention, hypokalemic alkalosis and suppression of renin and aldosterone.<sup>89-93, 106</sup> These abnormalities are corrected by stopping licorice ingestion. Carbenoxolone sodium is another derivative of glycyrrhetic acid. Similar abnormalities may occur when this drug is taken to aid gastric ulcer healing.<sup>9, 94, 97</sup>

**Low renin essential hypertension** Some 25 per cent of patients with apparently essential hypertension have suppressed levels of plasma renin.<sup>98-99</sup> and it has been suggested that these patients may have an excess of an as yet unidentified mineralocorticoid which leads to renin suppression and hypertension. Elevated levels of deoxycorticosterone and 18 OH deoxycorticosterone have been shown in a minority of such patients.

Particular circumstances certainly suggest the presence of mineralocorticoid excess. Patients with low renin essential hypertension have a lower salivary sodium/potassium ratio than do patients with hypertension associated with normal plasma renin.<sup>100</sup> They may show a more marked hypotensive response to the mineralocorticoid antagonist spironolactone than do those with normal renin values,<sup>91, 92</sup> as well as a more marked hypotensive response to the adrenal inhibitor aminoglutethimide.<sup>98</sup> These observations have been widely interpreted to indicate mineralocorticoid excess although other diuretics also seem more effective in lowering blood pressure in the low renin group.<sup>91, 92</sup> Spirk and colleagues<sup>101</sup> reported a greater hypotensive response to spironolactone than to a thiazide diuretic, an observation previously described in primary hyperaldosteronism.<sup>102</sup> In contrast to primary hyperaldosteronism, however, total exchangeable sodium is normal in low renin essential hypertension.<sup>9, 95</sup>

nine cases. A definitive pathological diagnosis was not reached in three patients who were excluded from the remainder of the analysis.

Mean plasma concentrations of aldosterone and tCO were significantly higher in the adenoma group while mean concentrations of potassium and renin were significantly lower compared with patients without adenoma (Fig 1). Mean plasma sodium was also higher while mean age and mean systolic and diastolic blood pressures were lower in the adenoma group but these differences did not reach statistical significance. However individual values for each of these variables overlapped (Fig 1) and straight forward analysis of preoperative data did not always enable a confident prediction of adrenal pathology. When the statistical technique of quadric analysis was applied complete separation of the adenoma and non adenoma groups was achieved (Fig 2).

The technique of quadric analysis was also applied to other published series of patients with primary hyperaldosteronism<sup>2,3</sup> again retrospectively. Quadrics were circumscribed about known adenoma and non adenoma groups in each series and the degree of separation was examined. Where quadrics overlapped patients we classified by likelihood ratio technique. With only two exceptions complete separation of the adenoma and non adenoma patients in each series was achieved. However when the data from these patients were examined relative to the quadrics of the original series<sup>1</sup> much less satisfactory separation was achieved. This illustrated that classification of individual patients with reference to quadrics established at another center is open to considerable error unless care is taken to standardize the biochemical measurements made in the laboratories concerned.

Since our original report<sup>1</sup> we have investigated and surgically explored a further 24 patients with primary hyperaldosteronism. A unilateral adenoma was found in 20 while in four further cases a tumor was not found the adrenal glands showing bilateral hyperplasia in each (Table II). Using quadric analysis adenoma was correctly predicted before operation in each of the 20 cases. Bilateral hyperplasia was correctly predicted in three of four cases but an adenoma was incorrectly predicted in the fourth.

Thus adrenal pathology has been correctly predicted before operation in 23 of 24 cases. The

**Table II** Results of quadric analysis used prospectively

| Patient initials | Pathological diagnosis | Quadric analysis prediction | Prediction odds |
|------------------|------------------------|-----------------------------|-----------------|
| E B              | Adenoma                | Adenoma                     | 89.5:1          |
| F D              | Adenoma                | Adenoma                     | 30.2:1          |
| F G              | Adenoma                | Adenoma                     | 5.7:1           |
| M F              | Adenoma                | Adenoma                     | 6.2:1           |
| W G              | Adenoma                | Adenoma                     | 5.1:1           |
| V G              | Adenoma                | Adenoma                     | 17.2:1          |
| M H              | Adenoma                | Adenoma                     | 10.5:1          |
| G H              | Adenoma                | Adenoma                     | 18:1            |
| T H              | Adenoma                | Adenoma                     | 4.9:1           |
| F J              | Adenoma                | Adenoma                     | 1.84:1          |
| J M              | Adenoma                | Adenoma                     | 1.5:1           |
| J O R            | Adenoma                | Adenoma                     | 2.7:1           |
| J R              | Adenoma                | Adenoma                     | 14.3:1          |
| L S              | Adenoma                | Adenoma                     | 6.6:1           |
| M S              | Adenoma                | Adenoma                     | 2.9:1           |
| M G              | Adenoma                | Adenoma                     | 22.8:1          |
| E T              | Adenoma                | Adenoma                     | 60.8:1          |
| A McD            | Adenoma                | Adenoma                     | 134.4:1         |
| H K              | Adenoma                | Adenoma                     | 49.7:1          |
| G Q              | Adenoma                | Adenoma                     | 16.3:1          |
| J W              | Non adenoma            | Adenoma                     | .6:1            |
| M K              | Non adenoma            | Non adenoma                 | 2.3:1           |
| A MCP            | Non adenoma            | Non adenoma                 | 18.3:1          |
| G T              | Non adenoma            | Non adenoma                 | 19.4:1          |

scarcity of patients without adenoma in this prospective group reflects our current bias against surgery in these patients.<sup>4</sup>

**2 Other statistical techniques** Recently Luetzsch and colleagues<sup>5</sup> used computer aided multiple logistic analysis of plasma potassium, plasma renin and urinary aldosterone to separate adenoma and non adenoma patients with primary hyperaldosteronism. By this means seven patients with an aldosterone producing adenoma were separated from four with bilateral adrenocortical hyperplasia. Thereafter adrenal pathology was correctly predicted in a further five cases.

Bighetti and colleagues<sup>6,7</sup> separated patients with and without adenoma by plotting basal recumbent plasma renin concentration against aldosterone excretion after sodium loading. Using linear discriminant analysis these workers correctly predicted adrenal pathology in a further 13 cases.

**3 Sodium loading with DOCA or fludrocortisone** Bighetti and associates<sup>6</sup> described the effects of sodium loading on aldosterone excre-

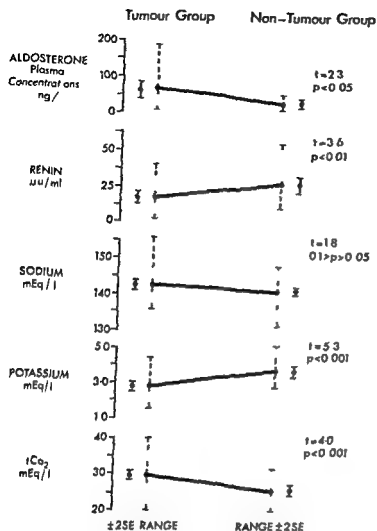


Fig 1 Comparison of biochemical variables in adenoma and non adenoma patients with primary hyperaldosteronism. Renin is expressed in terms of the International Reference Standard

**Differentiation of adenoma from bilateral hyperplasia** A large number of methods have been described for preoperative differentiation of patients with a unilateral adenoma from those with bilateral hyperplasia of the zona glomerulosa. These include statistical techniques such as quadric analysis<sup>127, 128</sup>, multiple logistic analysis<sup>129</sup> and linear discriminant analysis<sup>130, 131</sup>. Other methods include sodium loading with deoxy corticosterone<sup>12</sup> or fludrocortisone<sup>110, 112</sup>, comparison of postural<sup>129, 132</sup> and diurnal<sup>133, 134</sup> changes in plasma aldosterone and comparison of change occurring during treatment with spironolactone<sup>113, 114</sup>. The adrenal glands have been examined by venography<sup>130, 131</sup>, ultrasound,<sup>131</sup> and scintillation scanning<sup>15, 153</sup> while the aldosterone concentration in the effluent of each adrenal gland has been compared<sup>133, 14, 150, 154</sup>. These various methods are discussed in detail below.

**1 Quadric analysis** The statistical technique of quadric analysis has been described in detail

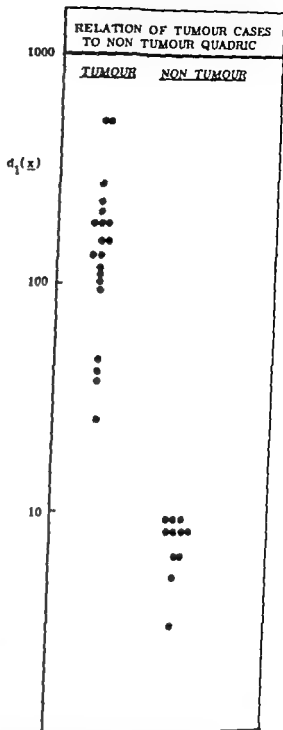


Fig 2 Differentiation of adenoma and non adenoma patients with primary hyperaldosteronism by quadric analysis. Retropective series (see text)

elsewhere.<sup>1, 7, 124</sup> The essence of the method is to combine data from individual patients and by so characterizing them to increase discrimination between patients of different pathological groups. We initially reviewed a group of 34 patients with hypertension, aldosterone excess and low plasma renin concentration.<sup>1, 7</sup> Twenty patients had a unilateral adrenocortical adenoma while no tumor was identified in eleven the adrenal glands showing hyperplasia of the zona glomerulosa in

nine cases. A definitive pathological diagnosis was not reached in three patients who were excluded from the remainder of the analysis.

Mean plasma concentrations of aldosterone and tCO were significantly higher in the adenoma group while mean concentrations of potassium and renin were significantly lower compared with patients without adenoma (Fig. 1). Mean plasma sodium was also higher while mean age and mean systolic and diastolic blood pressures were lower in the adenoma group but these differences did not reach statistical significance. However individual values for each of these variables overlapped (Fig. 1) and straight forward analysis of preoperative data did not always enable a confident prediction of adrenal pathology. When the statistical technique of quadric analysis was applied complete separation of the adenoma and non adenoma groups was achieved (Fig. 2).

The technique of quadric analysis was also applied to other published series of patients with primary hyperaldosteronism<sup>2-11</sup> again retrospectively. Quadrics were circumscribed about known adenoma and non adenoma groups in each series and the degree of separation was examined. Where quadrics overlapped patients were classified by likelihood ratio technique. With only two exceptions complete separation of the adenoma and non adenoma patients in each series was achieved. However when the data from these patients were examined relative to the quadrics of the original series much less satisfactory separation was achieved. This illustrated that classification of individual patients with reference to quadrics established at another center is open to considerable error unless care is taken to standardize the biochemical measurements made in the laboratories concerned.

Since our original report we have investigated and surgically explored a further 24 patients with primary hyperaldosteronism. A unilateral adenoma was found in 20 while in four further cases a tumor was not found the adrenal glands showing bilateral hyperplasia in each (Table II). Using quadric analysis adenoma was correctly predicted before operation in each of the 20 cases. Bilateral hyperplasia was correctly predicted in three of four cases but an adenoma was incorrectly predicted in the fourth.

Thus adrenal pathology has been correctly predicted before operation in 23 of 24 cases. The

**Table II** Results of quadric analysis used prospectively

| Patient initials | Pathological diagnosis | Quadric analysis prediction | Prediction odds |
|------------------|------------------------|-----------------------------|-----------------|
| E B              | Adenoma                | Adenoma                     | 89.5:1          |
| F D              | Adenoma                | Adenoma                     | 30.7:1          |
| F G              | Adenoma                | Adenoma                     | 5.3:1           |
| M F              | Adenoma                | Adenoma                     | 6.2:1           |
| W G              | Adenoma                | Adenoma                     | 117:1           |
| M G              | Adenoma                | Adenoma                     | 1.2:1           |
| M H              | Adenoma                | Adenoma                     | 10:1            |
| G H              | Adenoma                | Adenoma                     | 18:1            |
| T H              | Adenoma                | Adenoma                     | 48:1            |
| F J              | Adenoma                | Adenoma                     | 1.84:1          |
| J M              | Adenoma                | Adenoma                     | 15.5:1          |
| J O R            | Adenoma                | Adenoma                     | 2.4:1           |
| J R              | Adenoma                | Adenoma                     | 143:1           |
| L S              | Adenoma                | Adenoma                     | 686:1           |
| M S              | Adenoma                | Adenoma                     | 2.9:1           |
| M G              | Adenoma                | Adenoma                     | 22.8:1          |
| E T              | Adenoma                | Adenoma                     | 60.8:1          |
| A McD            | Adenoma                | Adenoma                     | 134.4:1         |
| H K              | Adenoma                | Adenoma                     | 49.7:1          |
| G Q              | Adenoma                | Adenoma                     | 18.3:1          |
| J W              | Non adenoma            | Adenoma                     | 5.1:1           |
| M K              | Non adenoma            | Non adenoma                 | 7.3:1           |
| A McP            | Non adenoma            | Non adenoma                 | 19.3:1          |
| G T              | Non adenoma            | Non adenoma                 | 194:1           |

scarcity of patients without adenoma in this prospective group reflects our current bias against surgery in these patients.

**2 Other statistical techniques** Recently Luetsher and colleagues<sup>1</sup> used computer aided multiple logistic analysis of plasma potassium, plasma renin and urinary aldosterone to separate adenoma and non adenoma patients with primary hyperaldosteronism. By this means seven patients with an aldosterone producing adenoma were separated from four with bilateral adrenocortical hyperplasia. Thereafter adrenal pathology was correctly predicted in a further five cases.

Biglieri and colleagues<sup>12</sup> separated patients with and without adenoma by plotting basal recumbent plasma renin concentration against aldosterone excretion after sodium loading. Using linear discriminant analysis these workers correctly predicted adrenal pathology in a further 13 cases.

**3 Sodium loading with DOCA or fludrocortisone** Biglieri and associates described the effects of sodium loading on aldosterone excretion

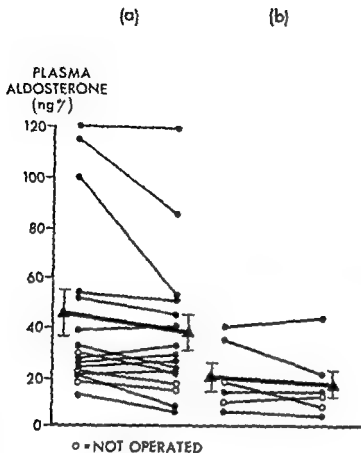


Fig 3 Plasma aldosterone before and during administration of 9 $\alpha$ -fludrocortisone in adenoma (a) and non adenoma (b) patients with primary hyperaldosteronism. Triangles with vertical bars represent means  $\pm$  SEM. Open circles represent unoperated patients whose adrenal pathology was predicted by quadric analysis.

tion. Deoxycorticosterone acetate (DOCA) for three days failed to alter aldosterone excretion in patients with an aldosterone producing adenoma but caused suppression in normals in patients with essential and renovascular hypertension and in those with primary hyperaldosteronism in whom a tumor was not found at operation. This seemed a useful maneuver for differentiating adenoma and non adenoma patients but it is now apparent that some of the latter also fail to suppress.<sup>111-113</sup> These workers also proposed that oral fludrocortisone (0.8 mg daily for 3 days) might distinguish primary from secondary hyperaldosteronism, as in the former aldosterone excretion was usually not suppressed.<sup>113</sup> However a slightly larger dose did cause aldosterone suppression in one of five patients with an aldosterone producing adenoma.<sup>110</sup>

We recently described the response of plasma aldosterone to fludrocortisone (0.8 mg daily for 3 days) in 22 patients with low renin hyperaldosteronism, with and without adenoma.<sup>110</sup> Although

basal aldosterone levels were often higher in adenoma patients, there was no significant change in mean values during treatment in either group (Fig 3). Furthermore the pattern of change did not differ among individual patients; an occasional response occurred in each group. We also studied patients with low renin and normal renin essential hypertension and hypertension associated with isolated deoxycorticosterone excess. Although plasma aldosterone decreased markedly in most patients an occasional increase occurred in each group.<sup>110</sup>

In our hands therefore this test was of little value in separating adenoma and non adenoma patients with primary hyperaldosteronism.

**4 Basal plasma renin plotted against aldosterone after fludrocortisone.** In another attempt to separate patients with primary hyperaldosteronism, with and without an adrenocortical tumor Biglieri and associates<sup>111</sup> plotted basal recumbent plasma renin concentration against the aldosterone excretion rate on the third day of sodium loading with deoxycorticosterone acetate. By this means they completely separated adenoma and non adenoma patients in a retrospective analysis and using these data they correctly predicted adrenal pathology in a further 13 patients.

We recently reported the relationship between basal plasma renin concentration and plasma aldosterone after fludrocortisone in 22 patients with low renin hyperaldosteronism.<sup>110</sup> The result is shown in Fig 4, no useful separation between tumor and non tumor groups was observed. This study differed from that of Biglieri and colleagues in using plasma levels of aldosterone rather than urinary excretion and the differential renin assay method.

**5 Plasma aldosterone postural change and diurnal variation.** The normal rise in plasma aldosterone on changing from the supine to the erect position also occurs in patients in the hyperplasia group but less markedly in patients with an aldosterone producing adenoma.<sup>114-116</sup> These differing responses to posture have been suggested as a method for distinguishing the two groups preoperatively.<sup>114-116</sup> Furthermore a diurnal variation in plasma aldosterone paralleling cortisol has been described in patients with an aldosterone producing adenoma but not among patients in the hyperplasia group.<sup>117</sup> It has been suggested that ACTH controls diurnal aldoster-

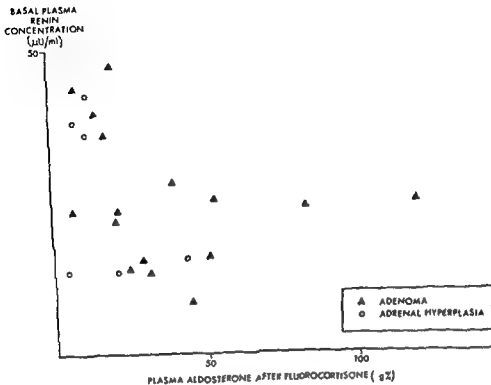


Fig 4 Basal plasma renin concentration plotted against plasma aldosterone after three days of 9α fluorocortisone in patients with primary hyperaldosteronism. Triangles represent adenoma and open circles non adenoma patients

one variation in patients with adenoma but not in those with hyperplasia

These differences in plasma aldosterone between the pathological groups are of considerable interest and emphasize the importance of measuring plasma aldosterone at fixed times and under defined conditions. However the value in differentiating individual patients with and without adenoma will be restricted by the exceptions that occur. Occasionally plasma aldosterone may increase on assuming an erect posture in patients in the adenoma group. Furthermore a fall in plasma aldosterone through the day is not invariable in patients with adenoma<sup>1</sup> and may also occur in patients with hyperplasia<sup>1</sup>.

**6 Response to spironolactone** Spark and Melby<sup>1</sup> reported a fall in blood pressure to normal during treatment with spironolactone in each of 20 patients subsequently shown to harbor an aldosterone producing adenoma. Two further patients with primary hyperaldosteronism in whom a tumor was not found at operation failed to show a blood pressure response fall during spironolactone. It seemed that the blood pressure

response to spironolactone might prove a useful guide to adrenal pathology. However in a larger series we found that a good hypotensive response to spironolactone can occur both in patients with and without adenoma.<sup>2</sup> Thus the blood pressure response to this drug is not of practical value in differentiating adenoma and non adenoma cases.

Ganguly and co workers<sup>3</sup> compared changes in renin and aldosterone during spironolactone therapy in patients with primary hyperaldosteronism with and without adenoma. The rise in plasma renin concentration was significantly greater in the non adenoma group. Plasma aldosterone also increased substantially in two of three patients but was unchanged in the adenoma group although it was unclear whether a similar dose was used. Schambelan and associates<sup>4</sup> reported similar findings.

We have been unable to confirm these observations. We found a consistent rise in plasma renin concentration during spironolactone treatment in both adenoma and non adenoma patients and the magnitude was similar in the two groups (Fig 5).



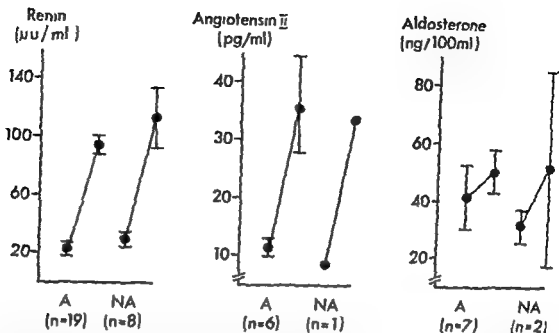


Fig 5 Changes in plasma concentrations of renin, angiotensin II and aldosterone in adenoma (A) and non adenoma (NA) patients with primary hyperaldosteronism during treatment with spironolactone (mean dose 320 mg/day in adenoma group and 260 mg/day in non adenoma group)

When measured plasma angiotensin II increased similarly (Fig 5). The changes in plasma aldosterone were more variable among seven patients with adenoma: values rose in four, fell in two, and were unchanged in one. Plasma aldosterone was measured before and during spironolactone therapy in two patients without tumor; in one there was a large rise and in the other a smaller fall. In our experience the renin, angiotensin, and aldosterone response to spironolactone appears similar in the two pathological groups.

Robertson<sup>11</sup> has pointed out that the greater responses in non adenoma patients reported by others would be expected if a standard spironolactone dose was used in the two groups. Patients without adenoma generally have less severe aldosterone excess so a greater correction of electrolytes and renin might occur. In our experience patients without adenoma generally require a somewhat smaller dose (Fig 5).

**7 Adrenal venography and adrenal vein sampling.** Localization of adrenocortical adenoma by retrograde injection of dye into the adrenal vein has been widely used.<sup>12-15</sup> Melby and colleagues<sup>12</sup> lateralized aldosterone producing adenomas too small to detect on venography, by measuring aldosterone concentrations in the venous effluent of each adrenal gland. Although technically difficult, the value of this procedure has also been confirmed.<sup>14, 15</sup>

The results of adrenal venography and adrenal

vein sampling for aldosterone measurement in some of the patients in this series have been reported.<sup>13, 14</sup> Among 14 patients with an aldosterone producing adenoma, subsequently confirmed at operation, the tumor was correctly identified in 11 (Fig 6) and suspected in two while catheterization was unsuccessful in the remaining patient. Five further patients had bilateral adrenocortical hyperplasia; a macronodule was identified on venography in one but was not distinguishable from an adenoma while in two further patients an adenoma was incorrectly suspected. Thus although adrenal venography was accurate in lateralizing adenomas, false positives were common among patients without tumor and a macronodule was indistinguishable from an adenoma.

Measurements of aldosterone in adrenal vein plasma were also valuable in lateralizing adenomas: the ratio between affected and unaffected sides ranging from 3 to 64 to 1. However, aldosterone concentration did not clearly separate normal and adenoma bearing glands and bilateral samples are not always obtainable for technical reasons.

The complications of adrenal venography have been stressed notably adrenal and iliac vein thrombosis and extravasation of contrast medium into the adrenal gland.<sup>16, 17</sup> Adrenal insufficiency followed venography in two of 58 patients in this series.<sup>13, 14</sup>

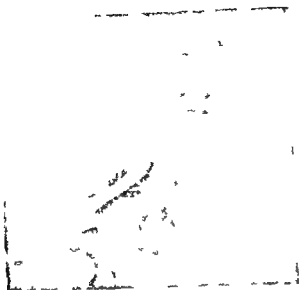


Fig 6A Left adrenal venogram in a patient with aldosterone producing adenoma

**8 Other radiological techniques** A plain abdominal film or pyelography may occasionally show renal displacement suggesting an adrenal carcinoma.<sup>1</sup> Retroperitoneal pneumography with tomograms of the adrenal area may reveal an irregularity in normal gland contour indicating the presence of an adenoma. However small tumors are not identified,<sup>2</sup> and because of the great variation in normal gland size adrenal hyperplasia can at best only be suspected. Furthermore this technique carries a small but appreciable risk of air embolism.<sup>3</sup>

The adrenal glands may sometimes be seen on aortography although this is variable and aldosterone secreting adenomas usually lack sufficient vascularity to be visible. Techniques for selective catheterization of the adrenal arteries have been described.<sup>4</sup> The value of this procedure has been limited by technical difficulties by the great variation in arterial supply and by the fact that each injection permits visualization of only a portion of the gland.<sup>5</sup> However Kahn and associates<sup>6</sup> successfully identified the adrenal abnormality in 19 of 20 patients with primary aldosteronism using the combined techniques of selective adrenal arteriography, adrenal venography and adrenal vein plasma sampling.

**9 Ultrasound** Ultrasound examination of the adrenal glands was undertaken in 10 patients in this series in whom an adenoma was identified at

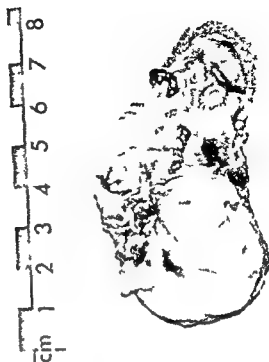


Fig 6B Left adrenal gland removed at operation from the same patient as in Fig 6A. Note an adrenocortical adenoma at the lower pole

venography.<sup>13</sup> The normal gland was not identifiable by the method used. Two adenomas were located of diameters 30 and 31 mm respectively. However early in the series an adenoma of diameter 35 mm was overlooked while seven tumors 10 to 25 mm in diameter were not identified. Davidson and colleagues<sup>14</sup> concluded that tumors greater than 30 mm in diameter should be identified with currently available commercial equipment in agreement with the findings of Burnholtz.<sup>15</sup>

**10 Scintillation scanning** The adrenal glands may also be visualized by scintillation scanning following intravenous <sup>131</sup>I 19 iodocholesterol which they actively concentrate.<sup>16</sup> Patients with aldosterone producing adenomas have been identified by concentration of radioactivity at the site of the tumor while a patient with bilateral hyperplasia showed diffuse adrenal uptake which unlike adenomas was suppressed by dexamethasone.<sup>17</sup> Recently Hogan and colleagues<sup>18</sup> and Conn and associates<sup>19</sup> differentiated patients with and without adenoma by repeated scanning without the use of dexamethasone. An adrenocortical adenoma was identified by an area of increased activity in 10 of 12 patients while an

asymmetrical uptake was uncommon in patients with hyperaldosteronism presumed due to adrenal hyperplasia and in low renin essential hypertension. Two patients with aldosterone excess and an adrenal carcinoma failed to show an increased uptake in their tumor.

This procedure as yet experimental, seems promising. Errors may occur because of uptake by related or overlying structures,<sup>13</sup> while the <sup>131</sup>I dose required is still large.<sup>13,14</sup> Recently a new scanning agent <sup>131</sup>I 6β iodomethyl 19 norcholesterol, was reported to have a higher adrenal uptake with improved images.<sup>15</sup>

**11 Other methods** Wotman and associates<sup>17</sup> reported that the potassium concentration in sublingual saliva was higher in patients with an aldosterone producing adenoma than in normals, in essential hypertension and in those with primary hyperaldosteronism associated with adrenal hyperplasia only. However the groups studied were small and the results showed a wide scatter; it seemed likely that with larger numbers some overlap would occur. There was no difference between the groups in the potassium concentration in parotid saliva.

Measurement of electrical potential difference across rectal mucosa has been proposed as a useful screening test for mineralocorticoid excess.<sup>18</sup> In our experience this technique is of limited usefulness and is unlikely accurately to differentiate adenoma and non adenoma patients with aldosterone excess.<sup>1</sup>

## Summary

Hypokalemia in a hypertensive patient is commonly diuretic induced. However, if hypokalemia persists after stopping diuretic therapy, possible mineralocorticoid excess including primary hyperaldosteronism must be considered. Hypertension with secondary hyperaldosteronism may occur with malignant phase hypertension and with renal or renovascular disease. However secondary hyperaldosteronism is associated with raised circulating levels of renin and angiotensin II while in primary hyperaldosteronism plasma concentrations of renin and angiotensin II are inappropriately low.

Hypertension and hypokalemia may also be associated with an excess of a mineralocorticoid other than aldosterone. Syndromes associated with an apparently isolated excess of 11 deoxycorticosterone or 18 hydroxy 11 deoxycorticosterone and of corticosterone have been described.

Plasma renin may be suppressed as in primary hyperaldosteronism but aldosterone values are normal or low. Hypertension, hypokalemia and renin suppression may also occur in Cushing's syndrome, associated with abnormalities of corticosteroid synthesis and during ingestion of licorice containing drugs. Again aldosterone values are normal or low.

Once the diagnosis of primary hyperaldosteronism has been confirmed, the rare cases of glucocorticoid remediable hyperaldosteronism and hyperaldosteronism associated with adrenal or ovarian carcinoma must be excluded. Thereafter, it is necessary to distinguish between the two commonest forms: a unilateral adrenocortical adenoma and bilateral hyperplasia of the zona glomerulosa. The statistical technique of quadric analysis used prospectively has correctly predicted adrenal pathology in 23 of 24 patients. Other methods for differentiating the two groups include comparisons of aldosterone response to sodium loading, comparison of postural and diurnal changes in plasma aldosterone, adrenal venography, and examination of the adrenal glands by ultrasound and by scintillation scanning.

## REFERENCES

1. Ferriss J B, Beevers D G, Brown J J, Davies D L, Fraser R, Lever A F, Mason P, Neville A M, and Robertson J I S. Clinical biochemical and pathological features of low renin (primary) hyperaldosteronism. *Am Heart J* 95:370-1978.
2. Ferriss J B, Beevers D G, Brown J J, Fraser R, Kremer D, Lever A F, and Robertson J I S. The treatment of low renin (primary) hyperaldosteronism. *Am Heart J* (In press).
3. Brown J J, Fraser R, Lever A F, and Robertson J I S. Aldosterone physiological and pathological variations in man. *Clin Endocrinol Metabol* 1:397-1972.
4. Brown J J, Davies D L, Lever A F, and Robertson J I S. Plasma renin concentration in human hypertension. 1. Relationship between renin, sodium and potassium. *Br Med J* 2:144-1963.
5. Reiman A S. The diagnosis of primary aldosteronism. *Boerhaave Course Hypertension*. Ed J de Graeff. Leyden 1973. Leyden University Press p 249.
6. Veyrat R, de Champlain J, Boucher R, and Genest J. Measurement of human arterial renin activity in some physiological and pathological states. *Can Med Assoc J* 90:21, 1964.
7. Helmer O M. Renin activity in blood from patients with hypertension. *Can Med Assoc J* 90:221-1964.
8. Barracrough M A, Bacchus B, Brown J J, Davies D L, Lever A F, and Robertson J I S. Plasma renin and aldosterone secretion in hypertensive patients with renal or renal artery lesions. *Lancet* 2:1310-1963.
9. Barracrough M A, Na H O. Depletion with acute malignant hypertension. *Am J Med* 40:263-1966.

- 10 del Greco F Simon N M Goodman E and Roguska J Plasma renin activity in primary and secondary hypertension *Medicine* 46 475 1967
- 11 Brown J J Matthew G K and Robertson J I S The effect of angiotensin on the function of the separate kidney in patients with unilateral renal artery stenosis *Clin Sci* 26 381 1964
- 12 Davies D L M.D. thesis University of London 19 2
- 13 Laragh J H Ulick S Januszewicz V Deming Q B Kelly W G and Lieberman S Aldosterone secretion and primary and malignant hypertension *J Clin Invest* 39 1091 1960
- 14 Fasciolo J C de Vito E Romero J C and Cucchi J N The renin content of the blood of humans and dogs under several conditions *Can Med Assoc J* 90 06 1964
- 15 Waite M A Circulating levels of angiotensin I in man measured by radioimmunoassay *Clin Sci* 42 20P 1972
- 16 Davies D L Schalekamp M A Beevers D G Brown J J Briggs J H Lever A F Medina A M Morton J J Robertson J I S and Tree M Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure *Lancet* 1 683 1973
- 17 Gill J R George J M Solomon A and Barter F C Hyperaldosteronism and renal sodium loss reversed by drug treatment for malignant hypertension *N Engl J Med* 270 1048 1964
- 18 McAllister R G Van Way C W Dayani A Anderson W J Temple E Michelakos A M Coppage W S and Oates J A Malignant hypertension: effect of therapy on renin and aldosterone *Circ Res* 28 and 29 (Suppl II) 160 1971
- 19 Gavras H Oliver N Aitchison J Begg C Briggs J D Brown J J Horton P W Lee F F Lever A F Prentice C and Robertson J I S Abnormalities of coagulation and the development of malignant phase hypertension *Kidney Int* 8 (Suppl 5) S 254 1975
- 20 Giese J Renin-angiotensin and hypertensive vascular damage: a review *Am J Med* 55 315 1973
- 21 Brown J J Curtis J R Lever A F Robertson J I de Wardener H E and Wing A J Plasma renin concentration and the control of blood pressure in patients on maintenance haemodialysis *Nephron* 6 39 1969
- 22 Brown J J Dusterdeck G Fraser R Lever A F Robertson J I S Tree M and Weir R J Hypertension and chronic renal failure *Br Med Bull* 27 123 1971
- 23 Schalekamp M A Beevers D G Briggs J D Brown J J Davies D L Fraser R Leibel M Lever A F Medina A Morton J J Robertson J I S and Tree M Hypertension in chronic renal failure: an abnormal relation between sodium and the renin-angiotensin system *Am J Med* 55 39 1973
- 24 Brown J J Brown W C B Fraser R Lever A F Morton J J Robertson J I S Agabiti Rosei E Tree M and Trust P M The effects of infusing the angiotensin II antagonist saralasin on arterial blood pressure and on the plasma concentrations of aldosterone renin and angiotensin II in normal subjects and in selected hypertensive patients. In: The systemic effects of antihypertensive agents, edited by M P Sambhu *Excerpta Medica Amsterdam* 1976 p 499
- 25 Robertson P W Kidjian A Harding L K Walters G Lee M R and Robb Smith A H T Hypertension due to a renin-secreting renal tumor *Am J Med* 43 963 1967
- 26 Kuhara I Katamura S Hoshino T Seida H and Watanabe T A hitherto unreported vascular tumour of the kidney. A proposal of juxtaglomerular cell tumour *Acta Pathol Jpn* 18 197 1968
- 27 Eddy R L and Sanchez S A Renin-secreting renal neoplasm and hypertension with hypokalemia *Ann Intern Med* 75 15 1971
- 28 Conn J W, Cohen E I Lucas C P McDonald W J Mayor M H Blough W M Eveland W C, Bookstein J I and Lapidus J Primary reninism *Arch. Intern Med* 130 68 1970
- 29 Bonnin J M Hodge R L and Lumbers E R A renin-secreting renal tumour associated with hypertension *Aust N Z J Med* 2 18 1972
- 30 Schambelan M Howes E L Stockigt J R Noakes C A and Biglieri E G Role of renin and aldosterone in hypertension due to a renin-secreting tumor *Am J Med* 55 86 1970
- 31 Brown J J, Fraser R Lever A F Morton J J Robertson J I S Tree M Bell P R F Davidson J K and Ruthven I S Hypertension and secondary hyperaldosteronism associated with a renin-secreting renal juxtaglomerular cell tumor *Lancet* 2 1228 1973
- 32 van Buchem F S P Doorenbos H and Elings H S Primary aldosteronism due to adrenocortical hyperplasia *Lancet* 2 337 1956
- 33 Thierien B Mellingner R C Caldwell J R and Howard P J Primary aldosteronism due to adrenal hyperplasia *Am J Dis Child* 88 90 1959
- 34 Kretschmer N Dickinson W A McNamara H and Karl R Primary aldosteronism in a 9 year old child *Pediatrics* 23 1115 1959
- 35 Genest J Kow E Beauregard P, Nowaczynski W Sandoz T Brouillet J Bolte E Verdy V and Marc Aurele J Electrolyte and corticosteroid studies in a 15-year-old girl with primary aldosteronism and malignant hypertension *Metabolism* 9 11 4 1960
- 36 Holten C and Petersen V P Malignant hypertension with increased secretion of aldosterone and depletion of potassium *Lancet* 2 918 1956
- 37 Barter F C and Biglieri E G Primary aldosteronism *Ann Intern Med* 48 647 1958
- 38 Moran W Goetz F C Melby J Zimmermann B and Kennedy J J Primary hyperaldosteronism without adrenal tumor *Am J Med* 28 638 1960
- 39 Conn J W Aldosteronism and hypertension *Arch Intern Med* 107 813 1961
- 40 Helmer O M and Judson W E Influence of high renin substrate levels on renin-angiotensin system in pregnancy *Am J Obstet Gynecol* 99 9 1967
- 41 Weir R J Pamtin D B Brown J J Fraser R Lever A F Robertson J I S and Young J A serial study in pregnancy of the plasma concentrations of renin, corticosteroids, electrolytes and proteins and of haematocrit and plasma volume *Br J Obstet Gynaecol* 78 590 1971
- 42 Weir R J Brown J J Fraser R Kraszewski A Lever A F McIlwaine G M Morton J J Robertson J I S and Tree M Plasma renin, renin substrate, angiotensin II and aldosterone in hypertensive disease of pregnancy *Lancet* 1 991 1973
- 43 Weir R J Brown J J Fraser R Lever A F Logan R W McIlwaine M Morton J J Robertson J I S and Tree M Relationship between plasma renin, renin substrate, angiotensin II, aldosterone and electrolytes in normal pregnancy *J Clin Endocrinol Metab* 40 108 1975

- 44 Brown J J Davies D L Doak P B Lever A F Robertson J I S and Trust P Plasma renin concentration in the hypertensive diseases of pregnancy Br J Obstet Gynaecol 73 410 1966
- 45 Gordon R D Symonds E M Wilmshurst E G and Pawsey C G K Plasma renin activity plasma angiotensin and plasma and urinary electrolytes in normal and toxæmic pregnancy including a prospective study Clin Sci Mol Med 45 115 1973
- 46 Weir R J Briggs E Mack A Taylor L Browning J Nasmith L and Wilson E Blood pressure in women after one year of oral contraception Lancet 1 467 1971
- 47 Weir R J Briggs E Mack A Nasmith L Taylor L and Wilson E Blood pressure in women taking oral contraceptives Br Med J 1 533 1974
- 48 Laragh J H Seeley J E Ledingham J C G and Newton M A Oral contraceptives renin aldosterone and high blood pressure JAMA 201 918 1967
- 49 Woods J W Oral contraceptives and hypertension Lancet 2 653 1967
- 50 Skinner S L Lumbers E R and Symonds E M Alteration by oral contraceptives of normal menstrual changes in plasma renin activity concentration and substrate Clin Sci 36 67 1969
- 51 Weir R J Tree M and Fraser R Effect of oral contraceptives on blood pressure and on plasma renin substrate and corticosteroids J Clin Pathol 23(Suppl 3) 49 1970
- 52 Weir R J Tree M and McElwee G Changes in blood pressure and in plasma renin substrate and angiotensin II concentrations in women taking contraceptive steroids Proceedings of the 4th International Congress of Endocrinology Washington Amsterdam 1973 Excerpta Medica p 1019
- 53 Weir R J Tree M Fraser R Chinn R H Davies D L Dusterdieck G O Robertson J I S Horne C H W and Mallinson A C Effect of combined oestrogen progestogen oral contraceptives and of their separate components on plasma level of renin renin substrate angiotensin and aldosterone and on blood pressure Proceedings of the 3rd International Congress on Hormonal Steroids James V H F and Martini L editors Amsterdam 1971 Excerpta Medica p 929
- 54 Weir R J Davies D L Fraser R Morton J J Tree M and Wilson A Contraceptive steroids and hypertension J Steroid Biochem 6 961 1975
- 55 Brown J J Ferriss J H Fraser R Lever A F Love D R Robertson J I S and Wilson A Apparently isolated excess deoxycorticosterone in hypertension a variant of the mineralocorticoid excess syndrome Lancet 2 243 1972
- 56 Oddie C J Coghlan J P and Scoggins B A Plasma deoxycorticosterone levels in man with simultaneous measurement of aldosterone corticosterone cortisol and 11 deoxycortisol J Clin Endocrinol Metab 34 1039 1972
- 57 Cope C L and Loizou S Deoxycorticosterone excretion in normal hypertensive and hypokalaemic subjects Clin Sci Mol Med 48 97 1975
- 58 Woods J W Little G W Stant E G Michelakis A M and Brill A B Effect of an adrenal inhibitor in hypertensive patients with suppressed renin Arch Int Med 123 366 1969
- 59 Melby J C Dale S L and Wilson T E 18 hydroxy deoxycorticosterone in human hypertension Circ Res 28 and 29(Suppl II) 143 1971
- 60 Brown R D and Strott C A Plasma deoxycorticosterone in man J Clin Endocrinol Metab 32 444 1971
- 61 Powell Jackson J D Cahn A Fraser R Grahame R Mason P Mussen G A K Powell Jackson P R and Wilson A Excess deoxycorticosterone secretion from adrenocortical carcinoma Br Med J 2 31 1974
- 62 Genest J and Nowaczynski W Aldosterone and electrolyte balance in human hypertension J R Coll Physicians Lond 5 77 1970
- 63 Fraser R James V H T Landon J Peart W S Rawson Annette Giles C A and McKay A M Clinical and biochemical studies of a patient with a corticosterone secreting adrenocortical tumour Lancet 2 1116 1968
- 64 Sennett J A Brown R D Island D P Yarbrow R L Watson J T Slaton P E Holthfield J W and Little G W Evidence for a new mineralocorticoid in patients with low renin essential hypertension Circ Res 36 and 37(Suppl I) 2 1975
- 65 Bighen E G Herron M A and Brust N 17 hydroxylation deficiency in man J Clin Invest 45 1916 1966
- 66 Goldsmith O Solomon D H and Horton R Hypogonadism and mineralocorticoid excess the 17 hydroxylase deficiency syndrome N Engl J Med 277 673 1967
- 67 Mallin S R Congenital adrenal hyperplasia secondary to 17 hydroxylase deficiency Ann Intern Med 70 69 1969
- 68 New M I Male pseudohermaphroditism due to 17a hydroxylase deficiency J Clin Invest 49 1970 1970
- 69 Binaire H Luiton J P Laudat P Legrand J C Turpin G Corvol P and Lemmer M A new male pseudohermaphroditism associated with hypertension due to a block of 17a hydroxylation J Clin Endocrinol Metab 35 67 1972
- 70 Tournare J Audi Parent L Loras B Blum J Castelnovo P and Forest M G Male pseudohermaphroditism with hypertension due to a 17a hydroxylation deficiency Clin Endocrinol 5 53 1976
- 71 Eberlein W R and Bongiovanni A M Congenital adrenal hyperplasia with hypertension unusual steroid pattern in blood and urine J Clin Endocrinol Metab 15 1531 1955
- 72 Baulieu E E Peillon F and Migeon C J Adrenal syndrome in The Adrenal Cortex Eisenstein A B ed London 1967 J & A Churchill Ltd p 553
- 73 Christy N P and Laragh J H Pathogenesis of hypokalaemic alkalosis in Cushing's Syndrome N Engl J Med 265 1053 1961
- 74 Krakoff L Nicols G and Amsel N Pathogenesis of hypertension in Cushing's Syndrome Am J Med 58 216 1975
- 75 Brown J J Davies D L Lever A F and Robertson J I S Plasma renin concentration in human hypertension II renin in relation to aetiology Br Med J 2 1215 1965
- 76 Bighen E G Slaton I E Schambelan M and Kronfeld S J Hypermineralocorticoidism Am J Med 45 170 1968
- 77 Schambelan M Slaton P F and Bighen F C Mineralocorticoid production in hyperadrenocorticism Am J Med 51 299 1971
- 78 Crane M G and Harris J J Deoxycorticosterone secretion rates in hyperadrenocorticism J Clin Endocrinol Metab 26 113 1966

- 9 Cost W S A mineralocorticoid excess syndrome presumably due to excessive secretion of corticosterone Lancet 1 367 1963
- 80 Molhuysen J A Gerbrandy J de Vries L A de Jong J C Lenstra J B Turner K P and Borst J G G A liquorice extract with deoxycortone like action Lancet 2 381 1950
- 81 Groen J Pelser H Frenkel M Hammung C E and Willebrands A F Effect of glycyrrhizic acid on the electrolyte metabolism in Addison's disease J Clin Invest 31 81 1957
- 82 Card W I Mitchell W Strong J A Taylor N R W Tompsett S L and Wil on J H G Effects of liquorice and its derivatives on salt and water balance Lancet 1 663 1953
- 83 Louis L H and Conn J W Preparation of glycyrrhizic acid the electrolyte active principle of licorice its effects upon metabolism and upon pituitary adrenal function in man J Lab Clin Med 47 10 1956
- 84 Salassa R M Mattox V R and Rosevear J W Inhibition of the mineralocorticoid activity of licorice by spironolactone J Clin Endocrinol Metab 22 1106 1967
- 85 Conn J W Rovner D R and Cohen E L Licorice induced pseudoadosteronism J A M A 205 497 1968
- 86 Doll R Hill I D and Hutton C F Treatment of gastric ulcer with carbenoxolone sodium and oestrogens Gut 6 19 1965
- 87 Turpie A G G and Thomson T J Carbenoxolone sodium in the treatment of gastric ulcer with special reference to side-effects Gut 6 591 1965
- 88 Kaplan N M Clinical hypertension New York 1973 Medcom Press
- 89 Dunn M J and Tannen H L Low renin hypertension kidney Int 5 317 1974
- 90 Adlin E V Channick B J and Marks A D Salivary sodium potassium ratio and plasma renin activity in hypertension Circulation 39 685 1969
- 91 Crane M G and Harris J J Effect of spironolactone in hypertensive patients Am J Med Sci 280 311 1970
- 92 Spark R F and Melby J C Hypertension and low plasma renin activity: presumptive evidence for mineralocorticoid excess Ann Intern Med 75 831 1971
- 93 Carey R M Douglas J G Schweikert J R and Liddle G W The syndrome of essential hypertension and suppressed plasma renin activity Arch Intern Med 130 849 1970
- 94 Distler A Keim H H Philipp T H Philipp A Walter U Werner E and Wolff H P Low renin hypertension: evidence for mineralocorticoid excess? In Hypertension—current problems Stuttgart 1974 Georg Thieme Verlag p 123
- 95 Adlin E V Marks A D and Channick B J Spironolactone and hydrochlorothiazide in essential hypertension Arch Intern Med 130 855 1970
- 96 Vaughan E D Laragh J E Gavras I Buhler F R Gavras H Brunner H R and Baer L Volume factor in low and normal renin essential hypertension Am J Cardiol 32 573 1973
- 97 Spark R F O'Hare C M and Regan R M Low renin hypertension Arch Intern Med 133 705 1974
- 98 Gwynup G and Steinberg T Differential response to thiazides and spironolactone in primary aldosteronism Arch Intern Med 120 436 1967
- 99 Lebel M Schalekamp M A Bevers D G Brown J J Davies D L Fraser R Kremer D Lever A F Morton J J Robertson J I S Tree M and Wilson A Sodium and the renin angiotensin system in essential hypertension and mineralocorticoid excess Lancet 2 308 1974
- 100 Schalekamp M A Lebel M Bevers D G Fraser R H Holsters G and Birkenhager W H Body fluid volume in low renin hypertension Lancet 2 310 1974
- 101 Jove A Crout J R and Kaplan N M Suppressed plasma renin activity in essential hypertension Ann Intern Med 72 9 1970
- 102 Padfield P L Bevers D G Brown J J Davies D L Lever A F Robertson J I S Schalekamp M A D Tree M and Titterton M Is low renin hypertension a stage in the development of essential hypertension or a diagnostic entity? Lancet 1 418 1975
- 103 Bevers D G Nelson C S Padfield P L Barlow D H Duncan G Greaves D A Hawthorne V M Morton J J Young D A R and Young J The prevalence of hypertension in an unselected population and the frequency of abnormalities of potassium angiotensin II and aldosterone in hypertensive subjects Acta Clin Belg 29 76 1974
- 104 Brown J J Lever A F Robertson J I S and Schalekamp M A Renal abnormality of essential hypertension Lancet 2 370 1974
- 105 Schalekamp M A Krauss V H Schalekamp-Koyken M I A Holsters G and Birkenhager W H Studies on the mechanism of hypernatremia in essential hypertension in relation to measurements of plasma renin concentration body fluid compartments and renal function Clin Sci 41 919 1971
- 106 Tuck M L Williams G H Cain J P Sullivan J M and Dluhy R G Relation of age diastolic pressure and known duration of hypertension to presence of low renin essential hypertension Am J Cardiol 32 637 1973
- 107 Padfield P L Allison M E M Brown J J Lever A F Luke R G Robertson C C Robertson J I S and Tree M Effect of intravenous frusemide on plasma renin concentration: suppression of response in hypertension Clin Sci Mol Med 49 353 1975
- 108 Grim C E Low renin "essential" hypertension: a variant of classic primary aldosteronism Arch Intern Med 135 347 1975
- 109 Gunnells J C McGuffin W L Robinson H R Grim C E Wells III Silver D and Glenn J F Hypertension: adrenal abnormalities and alterations in plasma renin activity Ann Intern Med 73 901 1970
- 110 Padfield P L Allison M E M Brown J J Ferriss J B Fraser R Lever A F Luke R G and Robertson J I S Response of plasma aldosterone to fludrocortisone in primary hyperaldosteronism and other forms of hypertension Clin Endocrinol 4 493 1975
- 111 Sutherland J A Ruse J L and Laidlaw J C Hypertension: increased aldosterone secretion and low plasma renin activity relieved by dexamethasone Can Med Assoc J 95 1109 1966
- 112 New M I and Peterson R E A new form of congenital adrenal hyperplasia J Clin Endocrinol Metab 27 300 1967
- 113 Maeda K Yoshinaga K Goto K Katsushima I Maebashi M Demura H Ino M Demura R and Tonkai T A case of glucocorticoid responsive hyperaldosteronism J Clin Endocrinol Metab 28 180 1968

- 114 Giehl G S Gotlin R W Biglieri E G and Katz F H A kindred with familial glucocorticoid suppressible aldosteronism *J Clin Endocrinol Metab* 37 715 1973
- 115 New M I Siegel E J and Peterson R E Dexamethasone suppressible hyperaldosteronism *J Clin Endocrinol Metab* 37 93 1973
- 116 Alterman S L Dominguez C Lopez Gomez A and Lieber A L Primary adrenocortical carcinoma causing aldosteronism *Cancer* 24 602 1969
- 117 Brown J I Ferriss J B Fraser R Lever A F and Robertson J I S Aldosterone excess and adrenal carcinoma *Br Med J* 1 686 1972
- 118 Foye L V and Feichtmeier T V Adrenal cortical carcinoma producing solely mineralocorticoid effect *Am J Med* 19 966 1955
- 119 Brooks R V McSwiney R R Prunty F T G and Wood F J Y Potassium deficiency of renal and adrenal origin *Am J Med* 23 391 1957
- 120 Zimmermann H Moran W H Rosenberg J C Kennedy B J and Frey R J Physiologic and surgical problems in the management of primary aldosteronism *Ann Surg* 150 653 1959
- 121 Conn J W Knopf R F and Nesbit R M Clinical characteristics of primary aldosteronism from an analysis of 145 cases *Am J Surg* 107 159 1964
- 122 Crane M G Harris J J and Herber H Primary aldosteronism due to an adrenal carcinoma *Ann Intern Med* 63 494 1965
- 123 Neville A M and Symington T Pathology of primary aldosteronism *Cancer* 19 1854 1966
- 124 Filipiecki S Feltynowski T Poplowska W Lapinska K Krus E Wocial B and Zaruszewicz W Carcinoma of the adrenal cortex with hyperaldosteronism *J Clin Endocrinol Metab* 35 225 1972
- 125 Ehrlich E N Dominguez O V Samuel L T Lynch D Oberhelman H and Warner N E Aldosteronism and precocious puberty due to an ovarian androblastoma (Sertoli cell tumour) *J Clin Endocrinol Metab* 23 338 1963
- 126 Todesco M Terrile V Borsatti A and Mantero F Primary aldosteronism due to a malignant ovarian tumour *J Clin Endocrinol Metab* 41 809 1975
- 127 Ferriss J B Brown J J Fraser R Kav A W Lever A F Neville A M O'Murcheartaigh I G Robertson J I S and Symington T Hypertension with aldosterone excess and low plasma renin pre-operative distinction between patients with and without adrenocortical tumour *Lancet* 2 905 1970
- 128 Aitchison J Brown J J Ferriss J B Fraser R Kay A W Lever A F Neville A M Symington T and Robertson J I S Quadratic analysis in the pre-operative distinction between patients with and without adrenocortical tumors in hypertension with aldosterone excess and low plasma renin *Am Heart J* 82 660 1971
- 129 Luetscher J A Ganguly A Melada G A and Dowdy A J Pre-operative differentiation of adrenal adenoma from idiopathic adrenal hyperplasia in primary aldosteronism *Circ Res* 34 and 35(Suppl 1) 175 1974
- 130 Stockigt J R Collins R D and Biglieri E G Determination of plasma renin concentration by angiotensin immunassay *Circ Res* 28 and 29(Suppl 1) 175 1971
- 131 Biglieri E G Stockigt J R and Schambelan M Adrenal mineralocorticoids causing hypertension *Am J Med* 52 623 1972
- 132 Biglieri E G Slaton P E Kronfeld S J and Schambelan M Diagnosis of an aldosterone producing adenoma in primary aldosteronism *JAMA* 201 510 1967
- 133 Biglieri E G Stockigt J R and Schambelan M A preliminary evaluation for primary aldosteronism *Arch Intern Med* 126 1004 1970
- 134 Ganguly A Dowdy A J Luetscher J A and Melada G A Anomalous postural response of plasma aldosterone concentration in patients with aldosterone producing adrenal adenoma *J Clin Endocrinol Metab* 36 401 1973
- 135 Ganguly A Melada G A Luetscher J A and Dowdy A J Control of plasma aldosterone in primary aldosteronism: distinction between adenoma and hyperplasia *J Clin Endocrinol Metab* 37 760 1973
- 136 Conn J P Tuck M L Williams G H Dluhy R G and Rosenoff S H The regulation of aldosterone secretion in primary aldosteronism *Am J Med* 53 67, 1972
- 137 Kem D C Weinberger M H Gomez Sanchez C Kramer N J Lerman R Furuya S and Nugent C A Circadian rhythm of plasma aldosterone concentration in patients with primary aldosteronism *J Clin Invest* 52 2272 1973
- 138 Schambelan M Brust N Chang H and Biglieri E G Aldosterone production in low renin hypertensive states: response to spironolactone therapy. Mechanisms of Hypertension. Proceedings of an International Workshop Conference (M P Sambhi ed) Amsterdam 1973 Excerpta Medica p 187
- 139 Bucht H Bergstrom J Lindholm B Wijnblad H J and Hokfelt M Catheterisation of the left adrenal vein for contrast injection and steroid analysis in a case of Conn's Syndrome *Acta Med Scand* 176 233 1964
- 140 Starer F Percutaneous suprarenal venography *Br J Radiol* 38 675 1965
- 141 Mikaelsson C G Retrograde phlebography of both adrenal veins *Acta Radiol* 6 345 1967
- 142 Reuter S R Blair A J Scheffert D F and Bookstein J J Adrenal venography *Radiology* 89 801 1967
- 143 Melby J C Spark R F Dale S L Egdahl R H and Kahn P C Diagnosis and localization of aldosterone producing adenomas by adrenal vein catheterization *N Engl J Med* 277 1000 1967
- 144 Sutton D Diagnosis of Conn's and other adrenal tumours by left adrenal phlebography *Lancet* 1 453 1968
- 145 Cope C Isard H J and Wesolowski W E Selective adrenal phlebography *Radiology* 90 1103 1978
- 146 Conn J W Royner D R Cohen E L Bookstein J J Cerny J C and Lucas C P Pre-operative diagnosis of primary aldosteronism *Arch Intern Med* 123 113 1969
- 147 Kahn P C Kelliker M D Egdahl R H and Melby J C Adrenal arteriography and venography in primary aldosteronism *Radiology* 101 71 1971
- 148 Scoggins B A Oddie C J Hare W S C and Coghlin J P Pre-operative lateralisation of aldosterone producing tumours in primary aldosteronism *Ann Intern Med* 76 891 1972
- 149 Horton R and Finck E Diagnosis and localisation in primary aldosteronism *Ann Intern Med* 76 880 1972
- 150 Mitty H A Nichols G L and Cabrolse J L Adrenal venography: clinical roentgenographic corre-

- lation in 80 patients *Am J Roentgenol* 119 564 19 3
- 171 Davidson J K Morley P Hurley G D and Holford N G H Adrenal venography and ultrasound in the investigation of the adrenal gland: an analysis of 68 cases *Br J Radiol* 48 435 1975
- 172 Conn J W Morita H Cohen E L Beierwaltes W H McDonald W J and Herwig K R Primary aldosteronism: photoscanning of tumours after administration of <sup>125</sup>I 19iodocholesterol *Arch Intern Med* 129 417 1972
- 173 Hogan M J McRae J Schambelan M and Bighetti G Location of aldosterone producing adenomas with <sup>125</sup>I 19iodocholesterol *Br J Med* 204 410 19 6
- 174 Holford N H G Davidson J K Brown J J Fraser R Lever A F and Robertson J I S Adrenal venography in the investigation of hypertension with hypokalaemia *Clin Endocrinol* (In press)
- 175 Distler A Barth C Roscher S Vecsei P Dhom G and Wolff H P Hochdruck und aldosteronismus bei solitären adenomen und bei nodularer hyperplasie der nebennierenrinde *Klin Wochenschr* 47 688 1969
- 176 George J M Wright L Bell N H and Bartter F C The syndrome of primary aldosteronism *Am J Med* 48 343 19 11
- 177 Baer L Sommers C Krakoff L R Newton M A and Laragh J H Pseudo primary aldosteronism: an entity distinct from true primary aldosteronism *Circ Res* 33 and 27(Suppl 1) 903 19 0
- 178 Rhamy H K McCoy R M Scott H W Fishman L M Mikelakis A M and Liddle G W Primary aldosteronism: experience with current diagnostic criteria and surgical treatment in fourteen patients, *Ann Surg* 167 718 1968
- 179 Lufkin E G Katz F H and Herman R H Primary aldosteronism due to hyperplasia of the zona glomerulosa: failure of suppression by DOCA or stimulation by angiotensin *Am J Med Sci* 264 367 19 7
- 180 Horton R Stimulation and suppression of aldosterone in plasma of normal man and in primary aldosteronism *J Clin Invest* 48 1230 1969
- 181 Spark F and Melby J C Aldosteronism in hypertension: the spironolactone response test *Ann Intern Med* 69 685 1968
- 182 Brown J J Davies D L Ferriss J B Fraser H Haywood E Lever A F and Robertson J I S Comparison of surgery and prolonged spironolactone therapy in patients with hypertension aldosterone excess and low plasma renin *Br Med J* 2 779 19 2
- 183 Robertson J I S In Discussion *Circ Res* 34 and 35(Suppl 1) 190 1974
- 184 Bayliss H I S Edwards O M and Starer F Complications of adrenal venography *Br J Radiol* 43 531 19 0
- 185 Melby J C Identifying the adrenal lesion in primary aldosteronism *Ann Intern Med* 76 1039 1972
- 186 Starer F The radiology of suprarenal masses, *Br J Hosp Med* 4 707 19 0
- 187 McLachlan M S F and Beales J S M Retroperitoneal venography in the investigation of adrenal diseases *Clin Radiol* 22 188 1971
- 188 Steinbach H L and Smith D R Extrapertoneal venography in diagnosis of retroperitoneal tumours *Arch Surg* 70 161 1955
- 189 Ransom C L Landes R R and McLelland R Air embolism following retroperitoneal pneumography: a nationwide survey *J Urol* 76 664 19 6
- 190 Lindvall N and Slezak I Arteriography of the adrenals *Radiology* 92 999 1969
- 191 Davidson J K Radiology in hypertension *Scott Med J* 15 153 19 0
- 192 Kahn P C and Nickerson L V Selective angiography of the adrenal glands *Am J Roentgenol* 101 739 1977
- 193 Rossi P Arteriography in adrenal tumours *Br J Radiol* 41 81 1969
- 194 Brnholz J C Ultrasound imaging of adrenal mass lesions *Radiology* 109 163 1973
- 195 Beierwaltes W H Lieberman L M, Ansari A N and Nishiyama H Visualization of human adrenal glands in vivo by scintillation scanning *J A M A* 216 975 1971
- 196 Sarkar H B Beierwaltes W H Ice R D Basmadjan G P Hetzel K H Kennedy W P, and Mason M M A new and superior adrenal scanning agent *NP 69 J Nucl Med* 16 1038 1975
- 197 Wotman S Baer L Mandel I D and Laragh J H Submaxillary potassium concentration in true and pseudoprimary aldosteronism *Arch. Intern Med* 126 748 19 0
- 198 Edmonds C J, and Richards, P Measurement of rectal electrical potential difference as an instant screening test for hyperaldosteronism *Lancet* 2 674 19 0
- 199 Bevers D G Morton J J Tree M and Young Jesse Rectal potential difference in the diagnosis of aldosterone excess *Gut* 18 36 19 5
- 200 Conn J W and Conn F R Primary aldosteronism versus hypertensive disease with secondary aldosteronism *Recent Prog Horm Res* 17 389 1961
- 201 Brown J J Brown W C B Fraser R Lever A F Morton J J Robertson J I S Rose E A, and Trust P M The effects of saralasin an angiotensin II antagonist on blood pressure and the renin angiotensin aldosterone system in normal and hypertensive subjects, *Aust N Z J Med* 6(Suppl 3) 46 19 6
- 202 Sekihara M Sennett J A Liddle G W, McKenna T J and Yarbrow L R Plasma 16  $\beta$  hydroxydehydroepiandrosterone in normal and pathological conditions in man *J Clin Endocrinol, Metab* 43 1078 19 6
- 203 Brown J J Fraser R Mason P A Morton, J J, Lever A F Robertson J I S Lee H A and Miller H Severe hypertension with lack of secondary sex characteristics due to partial 17  $\alpha$  hydroxylase deficiency *Scott Med J* 21 229 19 6
- 204 Brown J J Fraser H Leckie B Lever A F, Morton J J Padfield P L Semple P F and Robertson J I S The significance of renin and angiotensin in hypertension *Cardiovas Clin* (In press 1977)
- 205 Fraser H Brown J J Brown W C Ferriss J B Kennedy A Lever A F Mason P A, Morton J J, Nicholls M G, Ramsay L E Robertson J I S Schalekamp M A D and Wilson A The adrenal cortex and hypertension: some observations on a possible role for mineralocorticoids other than aldosterone *J Steroid Biochem* (In press)
- 206 Holmes A M Marrott P H Young J and Prentice E Pseudohyperaldosteronism induced by habitual ingestion of liquorice *Postgrad Med J* 46 625 19 0
- 207 Gunnells J C and McGuffin W L Low renin hypertension *Ann Rev Med* 26 59 1975
- 208 Conn J W Cohen H I and Herwig K R The dexamethasone modified adrenal scintiscan in hyporenemic aldosteronism (tumor versus hyperplasia) *A*



- 189 comparison with adrenal venography and adrenal  
venous aldosterone J Lab Clin Med 88 811 1976  
Bangham D R Robertson I Robertson J I S  
Robinson C J and Tree M An international colla-  
borative study of renin assay establishment of the  
International Reference preparation of Human Renin

- 190 Clin Sci Mol Med 48(Suppl 2) 137 1975  
Schamberlan M Brust N L Chang B C F Slater  
K L and Böhler H G Circadian rhythm and effect  
of posture on plasma aldosterone concentration in  
primary aldosteronism J Clin Endocrinol Metab  
43 115 1976

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

## Radionuclides in the assessment of myocardial infarction

Milton S Klein MD  
Robert Roberts MD  
R Edward Coleman MD\*  
St Louis Mo

Radionuclides in Cardiology have been used mainly for detection of myocardial infarction and assessment of left ventricular function.<sup>1</sup> The need for improved detection of myocardial infarction is related to the lack of sensitivity and specificity of the ECG or plasma enzymes in certain clinical conditions.<sup>2</sup> Diagnosis of infarction after cardiac surgery is particularly troublesome since even creatine phosphokinase isoenzymes specific for myocardial damage are consistently elevated as a result of the iatrogenic injury. The recent interest in protection of ischemic myocardium<sup>3</sup> requires measurement of infarct size and several studies suggest that quantification of infarct images may be possible<sup>4,5</sup> which has intensified the search for more appropriate radionuclides.

Four categories of radionuclides have been utilized to identify zones of ischemia or infarction as areas of decreased activity or cold spots: (1) Potassium analogs (<sup>41</sup>K, <sup>86</sup>Rb and more recently <sup>201</sup>Tl); (2) metabolic substrates (labeled free fatty acids <sup>15</sup>NH<sub>3</sub>); (3) inert gases (<sup>81</sup>Kr, <sup>133</sup>Xe); and (4) labeled microspheres or macroaggregates.<sup>6-8</sup> However, radionuclides which accumulate in areas of infarction (hot

spots)<sup>9</sup> offer some advantages over those which localize in normal tissue (cold spots). To date radiopharmaceuticals which produce cold spots cannot distinguish acute myocardial infarction from scar tissue, old infarction or ischemia.<sup>10,11</sup> Accordingly, this review will deal primarily with those agents which are taken up in the area of infarction.

Historically, the first studies to delineate myocardial infarction by a radionuclide accumulating in necrotic tissue utilized mercurial compounds.<sup>12</sup> Poor resolution and radiation risks precluded their extensive use clinically.<sup>13</sup> Subsequently, the serendipitous discovery that bone seeking radionuclides accumulate in myocardial infarcts initiated the widespread use of technetium labeled compounds for infarct imaging.<sup>14</sup>

The basis of a positive image is dependent on several factors: (1) the ratio of radioactivity in infarcted compared to normal myocardium which should generally be at least 4:1; (2) the ratio of radioactivity in myocardium to that of surrounding structures (liver, etc.); (3) the size of the infarct; and (4) the distribution and density of cell death (although the same number of myocardial cells may be necrotic in subendocardial as in transmural infarctions, the latter are more easily visualized scintigraphically because of the localization of counts in one area).

### Mercurial compounds

Mercurochrome has long been known to stain necrotic tissue and fluoresce under ultraviolet light.<sup>15</sup> Much of the early work in myocardial infarct imaging was performed using compounds labeled with radioactive mercury because of their stability and accumulation in necrotic tissue.<sup>16</sup> The first attempts to demonstrate radionuclide

From the Cardiovascular Division, Washington University School of Medicine, St. Louis, Mo, and the Department of Radiology, The Mallinckrodt Institute of Radiology, Washington University School of Medicine.

This study was supported in part by SCOR in Ischemic Heart Disease Grant P17 HL-17648 from the National Heart and Lung Institute, National Institutes of Health.

Received for publication March 29, 1977.

Reprint requests: Robert Roberts, MD, Director, Cardiac Care Unit, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, Mo. 63110.

Department of Radiology, University of Utah Medical Center, Salt Lake City, Utah.

- comparison with adrenal venography and adrenal  
venous aldosterone J Lab Clin Med 88 841 1976
- 189 Bangham D R Robertson I, Robertson J I &  
Robinson C J and Tree M An international colla-  
borative study of renin assay establishment of the  
International Reference preparation of Human Renin
- 190 Clin Sci Mol Med 48(Suppl 2) 135 1975  
Schamberlan M Brust N L Chang B C F Slater  
K L and Bigheri E G Circadian rhythm and effect  
of posture on plasma aldosterone concentration in  
primary aldosteronism J Clin Endocrinol Metab  
43 115 1976

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.

labeling of leukocytes with  $^{111}\text{In}$  8 hydroxyquinoline<sup>22</sup> This was accomplished without alterations in white blood cell viability or function When labeled leukocytes are administered to animals with experimental infarction images of the infarct can be obtained in dogs 24 hours after coronary occlusion Forty eight hours after infarction an increased number of counts were detected in the infarct zone compared to the normal myocardium Ratios of radioactivity of infarct compared to normal myocardium were 23:1

### Tetracycline

Since the mercurial compounds produce infarct images with poor resolution and since radiopharmaceuticals which accumulate in infarcts as a result of inflammation lack specificity investigators initiated studies with technetium-labeled tetracycline designed to improve sensitivity and specificity Like the mercurial compounds tetracycline fluoresces and accumulates in myocardial tissue undergoing necrosis<sup>23</sup> Immediately after intravenous administration tetracycline produces a yellow fluorescence in normal heart muscle but not in necrotic tissue However within the next three hours the intensity of fluorescence increases around the infarct border and is absent from normal tissue The mechanism of accumulation of  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline is thought to be related to binding of the tracer to protein in nucleic acids in necrotic myocardial cells Its accumulation appears to be influenced by free calcium accumulation in necrotic myocardium—a mechanism postulated for other radiopharmaceuticals as well<sup>24</sup> After three to four days fluorescence is seen only in the margin of the infarct and by seven days clumps of tracer are noted throughout the infarct With administration of 10 to 15 mCi of  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline intravenously 4 to 24 hours after acute myocardial infarction accumulation is primarily in the liver kidneys and gall bladder Four hours after infarction only one of four dogs had a scintigraphically demonstrable infarct By 24 hours however ratios of radioactivity in infarcts compared to normal myocardium ranged from 5:9 to 8:1 Hemorrhagic infarcts were more readily demonstrable by labeled tetracycline<sup>25</sup>

Early studies in patients<sup>26</sup> demonstrated that each of 14 patients with acute myocardial infarction had positive  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline images if

injected 24 hours after infarction and imaged 24 hours after injection All nine patients without acute infarction had negative images including several patients with old infarction Localization of infarction determined scintigraphically was concordant with electrocardiographic localization Also the correlation of infarct size (measured by peak total CPK) with images categorized as having large moderate or small infarcts scintigraphically was good ( $r = 0.84$ )

The sensitivity and specificity of  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline myocardial imaging is less impressive in other studies<sup>27</sup> Only 12 of 25 true positive and six of 11 true negative images were reported in one study<sup>28</sup> Other difficulties precluding the widespread clinical utility of  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline myocardial imaging include the following (1) the 24 hour delay from infarct to image precludes early infarct diagnosis (2) uptake of the tracer by the liver makes the accurate diagnosis of diaphragmatic infarction difficult (3) relatively small ratios of activity in infarcts compared to normal myocardium account for poor delineation of the infarct zone Hence  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline has not become a frequently used method of infarct imaging

### $^{99\text{m}}\text{Tc}$ -glucoheptonate

A major difficulty with most imaging agents in diagnosing acute myocardial infarction has been the delay in the production of an abnormal image Circumventing this problem by finding a radionuclide designed to permit early imaging would be of great importance One agent that appears to offer promise in detecting infarction sooner is  $^{99\text{m}}\text{Tc}$  glucoheptonate When this radionuclide was administered to nine dogs four hours after coronary occlusion the ratio of activity in infarcts compared to normal myocardium was 20:1 Concentration of the radionuclide in infarcts was somewhat dependent on blood flow since the greatest number of counts occurred when perfusion was 20 to 40 per cent of normal Early imaging was not significantly encumbered by overlay of radioactivity in skeletal structures or cardiac blood pool and ratios of radioactivity in infarcts compared to normal tissue were better than those seen with  $^{99\text{m}}\text{Tc}(\text{Sn})$  tetracycline but similar to those observed with  $^{99\text{m}}\text{Tc}(\text{Sn})$  pyrophosphate<sup>29,30</sup>

In one study of 27 patients with chest pain  $^{99\text{m}}\text{Tc}$  glucoheptonate was administered two to 48

accumulation in experimental myocardial infarcts *in vivo* were performed in 1962 using  $^{203}\text{Hg}$  chlormerodrin.<sup>10</sup> Fifteen of 16 dogs with coronary occlusions were shown to have abnormal scintigrams with a preponderance of counts in ischemic and necrotic myocardium compared with normal myocardium by direct counting of histologic specimens. Imaging of myocardial infarcts *in vitro* in pigs also demonstrated accumulation of  $^{203}\text{Hg}$  chlormerodrin as early as 12 to 24 hours after infarction but with optimal results at three to five days after infarction. Images were normal by 9 to 12 days.<sup>11</sup> Of even greater interest was the finding that coronary reperfusion was not necessary for accumulation of mercurial compounds in infarcts.<sup>12</sup> Studies in patients, however, have been disappointing.<sup>13</sup> Only three of 13 patients with myocardial infarctions were successfully imaged with  $^{203}\text{Hg}$  chlormerodrin four to eight days post infarction. In dogs it was necessary to administer 700  $\mu\text{Ci}$  but the 47 day half life of  $^{203}\text{Hg}$  and high radiation exposure to the liver and kidney precluded the use of high doses in humans. Thus the amount of activity accumulated in the myocardial infarcts was suboptimal for image production. Other mercurial compounds, however, have been shown to accumulate more avidly in myocardial infarcts.<sup>14</sup> For example  $^{203}\text{Hg}$  hydroxy mercury 4,5 dibromofluorescein has a ratio of activity in infarcts compared to normal myocardium of 100:1 while  $^{203}\text{Hg}$  chlormerodrin has a ratio of only 6:1. Although other radiopharmaceuticals have more recently taken the place of mercurial compounds in clinical use these radionuclides were instrumental in establishing that (1) tracers do accumulate in myocardial infarcts (2) they can be detected externally, and (3) accumulation occurs despite total occlusion of a coronary artery.

#### Iodinated compounds

Some early studies reported the accumulation of  $^{131}\text{I}$  in myocardial infarcts.<sup>15</sup> One study of 23 patients with acute myocardial infarction reported a 20 per cent greater number of counts localized over the left side of the chest when compared to the right side after oral administration of 50 to 200  $\mu\text{Ci}$  of  $\text{Na}^{131}\text{I}$ . Seven days after infarction however postmortem data revealed a ratio of radioactivity in infarcts compared to normal myocardium of only 1.7:1.<sup>16</sup> Subsequent studies demonstrated that the left precordial

activity probably represented  $^{131}\text{I}$  concentration in gastric secretions persisting in the stomach due to delayed gastric emptying seen in patients with recent myocardial infarctions.<sup>17</sup>

#### Gallium citrate

After it was recognized that mercurial radionuclides would not be beneficial in the clinical setting of infarct imaging, investigators turned to agents such as gallium citrate.<sup>18</sup> Gallium citrate is a radiopharmaceutical which accumulates in areas of inflammation and in certain tumors.<sup>19</sup> Since this radiopharmaceutical accumulates in white blood cells which are known to migrate to the periphery of acute infarctions, it seemed likely that "Gallium citrate would accumulate in regions of myocardial necrosis. When 3 to 4 mCi of "Gallium citrate were administered intravenously two days after transient occlusion of the left anterior descending coronary artery, accumulation of the radionuclide was noted in dogs with infarction (prolonged occlusion) but not with transient ischemia (less than 20 minute occlusions). Furthermore, *in vivo* and *in vitro* studies demonstrated a good correlation between the intensity of "Gallium uptake and the number of leukocytes seen histologically in the infarct zone as well as with the extent of myocardial CPK depletion.<sup>21</sup> However, "Gallium myocardial imaging has not been shown to be useful clinically. Since the ratio of radioactivity in infarcts compared to normal myocardium is relatively small compared to other radionuclides, one would expect rather poor sensitivity.<sup>22</sup> In one study, only five of eight patients with myocardial infarction demonstrated an abnormal image. It should be emphasized that "Gallium detects areas of inflammation and is, therefore, not specific for infarction. Hence, other disorders such as pericarditis might also be associated with an abnormal image. Accumulation of gallium by the liver makes recognition of diaphragmatic infarctions difficult. In addition, images do not become abnormal for several days, precluding early detection of infarction. Furthermore, since images remain abnormal for at least three weeks serial imaging is impossible.<sup>23</sup>

#### Indium labeled leukocytes

Further attempts to take advantage of the migration of leukocytes into infarcts for the purposes of myocardial imaging employed the

and specificity of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate in detecting acute myocardial infarction were excellent unless images were obtained more than seven days after infarction.<sup>23</sup> Localization of infarction by imaging compared with electrocardiograms was very good.

One large study of 101 patients with myocardial infarction demonstrated 96 abnormal images. The five patients with false negative images were all scanned more than seven days after infarction. Ninety-two of 101 patients without infarction had negative images. Of the remaining nine positive images, seven patients were thought to have unstable angina. A second study of 165 patients showed that 85 per cent with infarction based on electrocardiograms and elevated plasma MB CPK activity had positive images. There was a 7 per cent false positive rate, some of whom represented patients arriving in the Coronary Care Unit several days after infarction at a time when cardiac enzymes had returned to baseline but when images were still abnormal. In other studies  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate detected 17 of 17 true positives and seven of 10 true negatives. This tracer appears to display the greatest sensitivity and specificity and the highest quality images when compared to other technetium labeled compounds.<sup>4</sup>

$^{99m}\text{Tc}(\text{Sn})$  pyrophosphate images are also capable of detecting acute subendocardial infarction. Each of 17 patients with subendocardial infarction diagnosed by conventional diagnostic criteria had abnormal images which were either localized or faint diffuse abnormalities. This latter type of abnormality has been noted to be characteristic of non-transmural infarctions.<sup>5</sup>

Despite experimental data showing that transient coronary occlusions do not produce abnormal images, and that the location of accumulation of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate corresponds to the location of greatest calcium deposition (known to occur only in necrotic myocardium), the specificity of this radionuclide for detection of infarction remains controversial. Patients with unstable angina in the absence of injury appear to exhibit abnormal images. Evidence suggesting that ischemia per se is not associated with abnormal images is mounting. Fetal mouse hearts which were reversibly damaged by perfusion with solutions containing no glucose or oxygen for 24 hours at 37°C exhibited very little  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate accumulation. In contrast are

versible damage with hypoxia and hypoglycemia at 42°C was associated with 152 per cent greater activity at 24 hours compared with that noted after one hour.<sup>6</sup> Furthermore, patients undergoing maximal exercise stress tests do not exhibit abnormal  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate images.<sup>7</sup> Thus these images appear to be specific for infarction in this setting. In studies in our own laboratory (unpublished data) in patients with unstable angina in whom infarction is excluded by normal plasma MB CPK, abnormal images were generally not seen even if the tracer was injected at the time of chest pain or 24 hours later. These data suggest that many of the patients with positive images and a history of unstable angina actually have subendocardial infarctions.

Numerous causes of false positive  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate images have been reported including left ventricular aneurysms,<sup>8</sup> ventriculotomy scars from sump drains,<sup>9</sup> and calcified heart valves.<sup>10</sup> Whether or not images are abnormal in the presence of calcified valves may be related to the rate of calcium turnover, degree of calcium deposition, or blood supply to paravalvular tissue. Closed chest massage<sup>11</sup> and direct countershock in animals<sup>1</sup> and in patients<sup>12</sup> have been shown to be associated with abnormal images. This may be related to cardiac trauma or deposition of the radionuclide in necrotic chest wall muscles.

As previously mentioned, diffusely positive  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate images have been reported primarily in patients with unstable angina or subendocardial infarction.<sup>5</sup> However, the specificity of the diffusely positive image has been questioned. In preliminary studies, diffusely abnormal images were observed in some normal subjects.<sup>3</sup> Subsequent data from normal subjects given  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate intravenously revealed that a delay in clearance of the tracer from the cardiac blood pool in some patients was responsible for production of a diffusely positive image. These findings emphasize the need for delayed images (two hours) after injection of the tracer before a diffuse image is considered abnormal.<sup>1</sup>

Diagnosis of acute myocardial infarction at the time of cardiac surgery is frequently difficult. The conventional indices of infarction (history, cardiac enzymes, and electrocardiograms) may lack the usual specificity in the setting of recent surgery.<sup>13</sup> In a study of 50 patients undergoing

hours after chest pain and 12 of 15 patients with acute infarction exhibited abnormal images. Several false positive images were reported. Scintigraphically estimated infarct size correlated well with peak total CPK ( $r = 0.77$ ).<sup>34</sup> In another study,  $^{99m}\text{Tc}$  glucuheptonate detected only three of 13 true positives and two of two true negatives.<sup>35</sup> Thus, despite some encouraging experimental results, drawbacks of poor resolution, and poor sensitivity make  $^{99m}\text{Tc}$  glucuheptonate in infarct imaging less beneficial than other tracers presently in use.

### Bone seeking radionuclides

**Introduction** Bone seeking tracers were noted to accumulate in zones of acute myocardial infarction during routine bone scans.<sup>36</sup> Subsequently phosphate compounds labeled with technetium were found to be excellent indicators of acute myocardial necrosis, and are presently used extensively in many Coronary Care Units.

$^{99m}\text{Tc}(\text{Sn})$  pyrophosphate Some of the earliest studies utilizing bone seeking radionuclides were performed in dogs with experimental infarction given  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate. This tracer is a commonly used bone scanning agent. Technetium 99m with its 140 keV gamma rays and its short half life is well suited for nuclear medicine instrumentation.

The mechanism of accumulation of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate in acute infarction has not been unequivocally established. Electron dense deposits of calcium hydroxyapatite like crystals have been demonstrated in mitochondria of cardiac tissue which has undergone necrosis.<sup>37</sup> Administration of labeled calcium chloride showed deposition of the calcium in mitochondria within the infarct if coronary occlusion was prolonged and followed by a period of reperfusion.<sup>38</sup> Thus, accumulation of these crystals appears to be specific for infarction and is dependent on perfusion as well as necrosis. The presence of calcium hydroxyapatite deposits in mitochondria from myocardial infarct zones similar to those found in bone suggests a possible mode by which bone seeking radionuclides accumulate in (and thus, identify) regions of acute infarction. A donut like rim of increased radioactivity is seen frequently in experimental acute transmural infarctions and appears to correlate well with localization of calcium hydroxyapatite deposits in greatest concentrations.<sup>39</sup> Of 19 dogs with acute coronary

occlusion, all exhibited abnormal images at 24 to 48 hours after infarction. A progressive decline in radioactivity was noted when injections were performed from two to 13 days after infarction. Similarly, diminution in the calcium concentration in mitochondria from areas of infarction corresponded to the decreasing accumulation of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate as a function of time after infarction. Within two weeks after infarction, the major proportion of calcium deposits were replaced by granulation tissue. This finding suggests a relationship between the binding of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate and deposition of calcium deposits in mitochondria, however it is probably not the sole mechanism by which  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate accumulates in myocardial infarcts since the per cent of injected dose of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate and  $^{32}\text{P}$  labeled pyrophosphate was only ten to twentyfold greater in the mitochondria from infarct zones compared to normal areas. However, a two hundred to six hundredfold increase in counts from homogenates of whole myocardial infarcts compared to homogenates of mitochondria from the infarct suggested that substantial deposition of the radionuclide occurs in subcellular loci other than mitochondria.<sup>40</sup>

Since the pattern of accumulation of the tracer in transmural infarction corresponds to the location of densest migration of leukocytes to the periphery of the infarct, an alternative mechanism might be that phagocytosis of the radionuclide is responsible for the production of an abnormal image. However, administration of cyclophosphamide to dogs with acute infarction did not preclude the production of positive images despite marked leukopenia. Thus, phagocytosis of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate is an unlikely mechanism of accumulation.<sup>41</sup>

The specificity of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate for the detection of acute infarction has been studied by transient occlusion of the left coronary artery in dogs. In this model, ischemia in the absence of infarction was not associated with a positive image.<sup>42</sup>

In patients, injection of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate as early as 12 to 16 hours after infarction was associated with a positive image. Optimal images are obtained one to three days post infarction but remain positive consistently for seven days and are usually normal after two weeks. In one study of 23 patients, the sensitivity

has nearly a thirtyfold greater ratio of activity in bone compared to infarct when compared to that observed with  $^{99m}\text{Tc}$  polyphosphate. Thus Fluorine is not likely to be a useful tracer because of problems of resolution related to its avidity for bone. Kinetic studies<sup>11</sup> of  $^{99m}\text{Tc}$  polyphosphate and Fluorine demonstrate that both radionuclides are cleared from the blood pool in a biexponential manner. The first portion of the curve is thought to be due to rapid uptake by bone and the second portion is due to renal clearance. Fluorine clears faster from both portions of the curve since  $^{99m}\text{Tc}$  compounds bind to red blood cells and plasma  $\alpha_2$  globulins (80 per cent of plasma radioactivity with  $^{99m}\text{Tc}$  is protein bound compared to 15 per cent with Fluorine). Finally a comparison of the resolution and sensitivity of the images showed  $^{99m}\text{Tc}$  polyphosphate to be a superior radionuclide.<sup>12</sup>

#### Considerations for the future

Each of the radiopharmaceuticals mentioned have drawbacks. The ideal infarct imaging tracer would have the following properties:

- 1 High sensitivity and specificity for the diagnosis of acute infarction
- 2 Short half life permitting serial imaging
- 3 High infarct compared to normal tissue ratios of activity with little background activity
- 4 Early clearance from the blood pool
- 5 Early detection of acute infarction
- 6 Accurate estimation of infarct size
- 7 Non invasive administration (not requiring coronary injections)
- 8 Safety
- 9 Easy production of the tracer
- 10 Low cost

At present radiopharmaceuticals are being utilized primarily for the detection, sizing and localization of acute myocardial infarction. Perhaps a more detailed understanding of their mechanisms of accumulation will permit in depth study of the pathophysiology of the disease states and mechanisms of action of pharmacologic agents.

The authors wish to thank Mr Donald Berner for his technical assistance and Ms Karen Patrick and Ms Carole Goodell for the preparation of the manuscript.

#### REFERENCES

- 1 Haides H, Oldewurtel H A, Moschos C B and Regan T J. Evaluation of potassium-43 scintillation images

- during early myocardial ischemia in an animal model. *Circulation* 53:115, 1976
- 2 Zaret B L, Strauss H W, Hurley P J, Natarajan T K and Pitt B A. A non invasive scintiphotographic method for detecting regional ventricular dysfunction in man. *N Engl J Med* 284:1163, 1971
- 3 Gunnar R M, Pietras R J, Blackaller J, Dadmun S E, Szanto P H and Tobin J R, Jr. Correlation of vectorcardiographic criteria for myocardial infarction with autopsy findings. *Circulation* 35:158, 1967
- 4 Dixon S H, Jr, Fuchs J C A, and Ebert P A. Changes in serum creatine phosphokinase activity. *Arch. Surg.* 103:66, 1971
- 5 Klein M, Coleman R E, Weldon C S, Sobel B E and Roberts H. Concordance of electrocardiographic and scintigraphic criteria of myocardial injury after cardiac surgery. *J Thorac Cardiovasc Surg* 71:934, 1976
- 6 Braunwald H. Protection of the ischemic myocardium. *Circulation* 53 (Suppl. I) March 1976
- 7 Holman B L, Lesch M, Zwerman F G, Temple J, Lowin H and Gorlin R. Detection and sizing of acute myocardial infarcts with  $^{99m}\text{Tc}(\text{Sn})$  tetracycline. *N Engl J Med* 291:159, 1974
- 8 Botwinick E H, Shames D, Lippin H, Tyberg J V, Townsend R and Parmley W W. Non invasive quantitation of myocardial infarction with technetium 99m pyrophosphate. *Circulation* 52:909, 1975
- 9 Holman B L. Selective uptake of radiopharmaceuticals by acutely infarcted myocardium. In: *Cardiovascular nuclear medicine*, Strauss H W, Pitt B and James A E Jr, eds. St Louis 1974. The C V Mosby Company p 276
- 10 Carr E A Jr, Beerwaltes W H, Patno M E, Bartlett J D and West A V. The detection of experimental myocardial infarcts by photoscanning. *AM HEART J* 64:650, 1962
- 11 Hurley P J, Cooper M, Reba R C, Foggenburg K J and Wagner N H Jr. KCl: A new radiopharmaceutical for imaging the heart. *J Nucl. Med.* 12:516, 1971
- 12 Romhild D W, Adolph R J, Sodd V C, Levenson M I, August L E, Nishiyama H and Berke R A. Cesium 129 myocardial scintigraphy to detect myocardial infarction. *Circulation* 48:1242, 1973
- 13 Martin, N D, Zaret B L, McGowan R L, Wells H P Jr and Flamm M D. Rubidium 81: A new myocardial scanning agent. *Radiology* 144:651, 1974
- 14 Strauss H W, Harrison M, Langan J K, Lebowitz E and Pitt B. Thallium 201 for myocardial imaging: relation of Thallium 201 to regional myocardial perfusion. *Circulation* 51:641, 1975
- 15 Evans J R, Gunton R W, Baker H G, Beanlands D S and Spears J C. Use of radioiodinated fatty acid for photoscans of the heart. *Circ Res* 16:1, 1965
- 16 Holman B L, Cohn P F, See J R, Idome J and Adams D F. Measurement of regional myocardial blood flow with Xe 133 both at rest and after contrast hyperemia (Abstract). *J Nucl. Med.* 16:536, 1975
- 17 Badinger H F, Yano Y and Hoop B. A comparison of Rb-48 and NH for myocardial positron scintigraphy. *J Nucl. Med.* 16:429, 1975
- 18 Ashburn W L, Braunwald E, Simon A L, Peterson K L and Gault J H. Myocardial perfusion imaging with radioactive labeled particles injected directly into the coronary circulation of patients with coronary artery disease. *Circulation* 44:851, 1971
- 19 Ritchie J L, Hamilton G W, Gould K L, Allen D, Kennedy J W and Hammermeister K. Myocardial imaging with indium 113m and technetium 99m



coronary artery bypass surgery,<sup>5</sup> there was a 16 per cent incidence of perioperative myocardial infarction judged by development of new Q waves and associated in each case with an abnormal <sup>99m</sup>Tc(Sn) pyrophosphate image. This group included some patients with pre surgical or perioperative bundle branch block, and underscored the fact that not all new bundle branch blocks should be interpreted as resulting from a fresh infarction. All patients with or without infarction exhibited elevated MB CPK activity. Thus plasma enzyme elevations could not be used to detect infarction and ischemic injury in patients with operative trauma to the heart. Since the electrocardiogram in this setting may also occasionally be equivocal, infarct imaging may be particularly useful as a specific index for the diagnosis of infarction.

Potential clinical uses for <sup>99m</sup>Tc(Sn) pyrophosphate myocardial imaging include the diagnosis of (1) subendocardial infarction, (2) infarction in the presence of ventricular conduction disturbances, (3) recent infarction at a time when cardiac enzymes have returned to baseline, and (4) perioperative infarction (especially after coronary artery bypass surgery).

Quantification of myocardial infarct size with radionuclides is being actively pursued experimentally and clinically but results at present are inconclusive. Good correlations have been obtained when anterior wall infarcts in dogs were imaged with a gamma camera grid and computer interface 48 hours after infarction and images were compared with gross infarct weight at post mortem ( $r = 0.87$ ). The best correlations were obtained with the left anterior oblique view grid computations *in vivo* and infarct weight ( $r = 0.92$ ).<sup>6</sup> Planimetry of infarct image area and correlating results with peak total CPK<sup>7</sup> in patients, or infarct weight estimated from morphology in dogs ( $r = 0.914$ ) has been quite successful.<sup>8</sup> Myocardial CPK depletion in experimental infarction also correlates with tissue <sup>99m</sup>Tc(Sn) pyrophosphate activity ( $r = 0.89$ ).<sup>9</sup>

Studies of patients have been less impressive however.<sup>10</sup> Use of <sup>99m</sup>Tc(Sn) pyrophosphate images in patients to categorize infarcts into large, medium or small groups failed to provide good correlations with peak total CPK or enzymatically estimated infarct size.<sup>11</sup> Of 27 patients with myocardial infarction, <sup>99m</sup>Tc(Sn) pyrophosphate image areas correlated poorly with maxi-

mal precordial ST segment elevation ( $r = 0.39$ ) or with the sum ST segment elevation ( $r = 0.47$ ). In general infarct size is difficult to quantify in locations other than anterior. Since the ratio of <sup>99m</sup>Tc(Sn) pyrophosphate activity in infarcts compared to normal myocardium was related to both the extent of necrosis and the degree of perfusion (as judged by injections of labeled microspheres in dogs with infarcts) merely measuring the number of counts in an area of infarct may not reflect infarct size alone.<sup>1</sup> Hence, the markedly decreased flow to the necrotic center of an infarct is associated with only modest sequestration of <sup>99m</sup>Tc(Sn) pyrophosphate. Also, problems related to overlap of bone resolution and sizing of three dimensional structures with a two dimensional system, all make infarct sizing less than optimal.

#### Other bone scanning radiopharmaceuticals

<sup>99m</sup>Tc(Sn) polyphosphate has similar physicochemical properties to those of <sup>99m</sup>Tc(Sn) pyrophosphate.<sup>12</sup> <sup>99m</sup>Tc polyphosphate has been shown to accurately detect both transmural and subendocardial infarction in patients three to 20 days after infarction.<sup>13</sup> As with <sup>99m</sup>Tc(Sn) pyrophosphate, correlations of scintigraphic localization of infarction with electrocardiographic localization is quite good. Understanding some of the physicochemical properties of the tracer affords some insight into potential causes of false positive or false negative results. Molecular weights of <sup>99m</sup>Tc polyphosphate between 4,000 and 6,000 daltons are optimal for imaging.<sup>14</sup> Weights greater than 8,000 confer colloidal properties associated with localization of the tracer in the reticuloendothelial system. Weights less than 3,000 promote rapid renal clearance and little bone deposition. Since <sup>99m</sup>Tc(Sn) polyphosphate (like other technetium compounds) are made by reduction of <sup>99m</sup>Tc pertechnetate to <sup>99m</sup>Tc by SnCl<sub>2</sub>, 2 H<sub>2</sub>O ideal ratios of polyphosphate to tin have been established. Ratios of 25:1 are optimal since less tin produces inefficient labeling and excess tin confers colloidal properties. Also, the solid state of tin promotes greater complex stability since polyphosphate degrades at pH > 10.<sup>15</sup>

A comparison of <sup>99m</sup>Tc polyphosphate with <sup>99m</sup>Tc(Sn) pyrophosphate in dogs with infarcts demonstrated ratios of radioactivity in infarcts compared to normal myocardium that were similar.<sup>16</sup> Fluorine another bone scanning agent

- R False positive myocardial infarct images due to delayed removal of  $^{99m}\text{Tc}(\text{Sn})$  pyrophosphate from the blood pool (Abstract) *Clin Res* 24 274A 1976
- 55 Alderman E L, Matloff H J, Shumway N E., and Harrison D C Evaluation of enzyme testing for the detection of myocardial infarction following direct coronary surgery *Circulation* 48 135 1973
  - 56 Bassan M M, Oatfield R, Hoffman I, Matloff J and Swan H J C New Q waves after aortocoronary bypass surgery *N Engl J Med* 290 349 1974
  - 57 Harris R A, Parkey R W, Bonte F J, Stokely E M, Buja L M and Willerson J T Sizing acute myocardial infarction in patients utilizing technetium stannous pyrophosphate myocardial scintigrams (Abstract) *Clin Res* 1 3A 1975
  - 58 Willerson J T, Parkey R W, Buja L M, Harris R A, Stokely E M, Blomqvist G and Bonte F J Sizing acute myocardial infarction utilizing technetium stannous pyrophosphate myocardial scintigrams in dogs and man (Abstract) *Circulation* 51 and 52 (Suppl II) 108 1975
  - 59 Tomanek R J, Marcus M L, Ehrhardt J C, Kerber R E., and Brown D D Technetium pyrophosphate uptake in infarcted cardiac muscle and relative importance of extent of necrosis and myocardial perfusion (Abstract) *Am J Cardiol* 37 177 1976
  - 60 Dewanjee M K, Fletcher J W., and Davis M A Chemical properties and biologic distribution of technetium tin polyphosphates (Abstract) *N Nucl Med* 13 427 1972
  - 61 McLaughlin P., Coates, G, Wood D, Craddock T., and Morch J Detection of acute myocardial infarction by technetium  $99m$  polyphosphate *Am J Cardiol* 35 330 1975
  - 62 Bonte F J, Parkey R W, Graham K H and Moore J G Distributions of several agents useful in imaging myocardial infarcts *J Nucl Med* 16 132, 1975
  - 63 Krishnamurthy G T, Thomas P B, Tubis M., Endow J S, Pritchard J H and Blahd W H Comparison of  $^{99m}\text{Tc}$  polyphosphate and  $^{99m}\text{Tc}$  kinetics, *J Nucl Med* 15 832 1974
  - 64 Krishnamurthy G T, Walsh C F, Shoop L E, Berger H G and Blahd, W H Comparison of  $^{99m}\text{Tc}$  polyphosphate and  $^{99m}\text{Tc}$  imaging *J Nucl Med* 15 837 1974

- macroaggregated albumin. New procedures for identification of stress induced regional ischemia. *Am J Cardiol* 35:380 1975
- 20 Parkey R W, Bonte F J, Meyer S L, Atkins J M, Curry G L, Stokely E M, and Willerson J T. A new method for radionuclide imaging of acute myocardial infarction in humans. *Circulation* 50:540 1974
  - 21 Malek P, Vavrejn H, Ratusky J, Kronrad L, and Kolc J. Detection of myocardial infarction by *in vivo* scanning. *Cardiology* 51:22 1967
  - 22 Bonte F J, Parkey R W, Graham K D, Moore R T, and Stokely M. A few method for radionuclide imaging of myocardial infarcts. *Radiology* 110:473 1974
  - 23 Hubner P J. Radiosotope detection of experimental myocardial infarction using mercury derivatives of fluo rescein. *Cardiovasc Res* 4:509 1970
  - 24 Gorten R J, Hardy L B, McCrow B H, Stokes J R, and Lumb G D. The selective uptake of  $Hg^{2+}$  chlormerodrin in experimentally produced myocardial infarcts. *Am Heart J* 72:71 1966
  - 25 Ramnathan P, Ganatra T, Daulatram K, Sen P K, and Blau M. Uptake of  $Hg$  hydroxy mercury fluoresein in myocardial infarcts. *J Nucl Med* 12:641 1971
  - 26 Carr E A, Cafruny E J, and Bartlett J D. Evaluation of  $Hg$  chlormerodrin in the demonstration of human myocardial infarcts by scanning. *Univ Michigan Med Bull* 29:27 1963
  - 27 Malek P, Ratusky J, Vavrejn H, Kronrad L, and Kolc J. Ischaemia detecting radiopaque substances for scanning cardiac and skeletal muscle. *Nature (London)* 214:1130 1967
  - 28 Dreyfus F, Ben Porath M, and Menezel J. Radioiodine uptake by the infarcted heart. *Am J Cardiol* 6:237 1960
  - 29 Mason D T, Frye H L, and Wagner H N. Radioisotope scanning of the precordial distribution of iodine in patients with myocardial infarction. *Circulation* 24:1338 1961
  - 30 Edwards C L, and Hayes R L. Tumor scanning with Gallium citrate. *J Nucl Med* 10:103 1969
  - 31 Kramer R J, Goldstein R E, Hirshfeld J W, Roberts W C, Johnston G S, and Epstein S E. Accumulation of gallium 67 in regions of acute myocardial infarction. *Am J Cardiol* 33:881 1974
  - 32 Zeman F G, Holman B L, O'Keefe A, and Idoune J. Selective uptake of  $^{99m}Tc$  complexes and Ga in acutely infarcted myocardium. *J Nucl Med* 16:975 1975
  - 33 Ahmed S A, Weiss E E, Thacker M, Welch M J, Coleman R E, Ter Pogossian M M, and Sobel H E. Externally monitored leukocyte infiltration in myocardial infarct (Abstract). *Am J Cardiol* 37:116 1976
  - 34 Malek P, Kolc J, Zastava V L, Zac F, and Peleska B. Fluorescence of tetracycline analogues fixed in myocardial infarction. *Cardiology* 42:303 1963
  - 35 Holman B L, Dewanjee M K, Idoune J, Fliegel C P, Davis M A, Treves S, and Eldh P. Detection and localization of experimental myocardial infarction with  $^{99m}Tc$  tetracycline. *J Nucl Med* 14:595 1973
  - 36 Lesch M, Tanaka T, and Holman B L. Comparative accuracy of  $^{99m}Tc$  pyrophosphate,  $^{99m}Tc$  tetracycline and  $^{99m}Tc$  glucoheptonate for the scintigraphic diagnosis of acute myocardial infarction (Abstract). *Circulation* 51 and 52 (Suppl II):53 1975
  - 37 Rossman D J, Strauss H W, Siegel M E, and Pitt B. Accumulation of  $^{99m}Tc$  glucoheptonate in acutely infarcted myocardium. *J Nucl Med* 16:875 1975
  - 38 Rossman D J, Rouleau J, Strauss H W, and Pitt B. Detection and size estimation of acute myocardial infarction using  $^{99m}Tc$  glucoheptonate. *J Nucl Med* 16:990 1975
  - 39 DiAlostinio A N. An electron microscopic study of cardiac necrosis produced by 8 a fluorocortisol and sodium phosphate. *Am J Pathol* 45:633 1964
  - 40 Shen A C, and Jennings R II. Kinetics of calcium accumulation in acute myocardial ischemic injury. *Am J Pathol* 67:441 1972
  - 41 Buja L M, Parkey R W, Dees J H, Stokely E M, Harris II A, Bonte F J, and Willerson J T. Morphologic correlates of technetium 99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs. *Circulation* 52:596 1975
  - 42 Klein M S, Coleman R E, Ahmed S A, Weiss E E, Roberts R, and Sobel H E.  $^{99m}Tc(Sn)$  pyrophosphate scintigraphy: sensitivity, specificity and mechanisms (Abstract). *Circulation* 51 and 52 (Suppl II):57 19 5
  - 43 Coleman R E, Klein M S, Roberts R, and Sobel H E. Improved detection of myocardial infarction with  $^{99m}Tc(Sn)$  pyrophosphate and serum MB CPK. *Am J Cardiol* 37:732 1976
  - 44 Willerson J T, Parkey R W, Bonte F J, Meyer S L, Atkins J M, and Stokely E M. Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. *Circulation* 51:1049, 1975
  - 45 Willerson J T, Parkey R W, Bonte F J, Meyer S L, and Stokely E M. Acute subendocardial myocardial infarction in patients—its detection by technetium 99m stannous pyrophosphate myocardial scintigrams. *Circulation* 51:436 1975
  - 46 Schelberg H, Ingwall J, Sybers H, and Ashburn W. Infant imaging agents in fetal mouse hearts after reversible and irreversible injury (Abstract). *Circulation* 51 and 52 (Suppl II):70 1975
  - 47 Klein M S, Coleman R E, Roberts R, and Weiss A N.  $^{99m}Tc(Sn)$  pyrophosphate scintigrams in exercise induced angina and calcified valves (Abstract). *Am J Cardiol* 37:149 1976
  - 48 Ahmad M, Dubiel J P, Vernon T A, and Martin R. Technetium 99m stannous pyrophosphate myocardial imaging in patients with and without left ventricular aneurysm. *Circulation* 53:833 1976
  - 49 Ahmad M, Dubiel J P, Logan K, Verdon T, and Martin R. Myocardial uptake of technetium 99m stannous pyrophosphate in patients with previous coronary artery bypass graft surgery (Abstract). *Circulation* 51 and 52 (Suppl II):148 1975
  - 50 O'Rourke R, Righetti A, Schelbert H, Daily P, Ashburn W, and Ross J Jr. Usefulness of pre and post operative  $Tc$  99m pyrophosphate scans in cardiac surgical patients (Abstract). *Am J Cardiol* 37:161 1976
  - 51 Mayorga Cortes A, Campeau R J, Sheps D, Gotthieb S, Mule A Jr, and Myerburg R J. Value and limitations of  $^{99m}Tc$  stannous pyrophosphate myocardial imaging in acute subendocardial infarction (Abstract). *Circulation* 51 and 52 (Suppl II):214 1975
  - 52 DiCola V H, Freedman G S, and Zaret H L. Effect of direct current countershock upon myocardial technetium 99m stannous pyrophosphate uptake (Abstract). *Am J Cardiol* 37:131 1976
  - 53 Pugh B R, Parkey R W, Bonte F J, Poliner L, Buja L M, and Willerson J T. Cardioversion and its potential role in the production of "false positive" technetium 99m stannous pyrophosphate myocardial scintigrams (Abstract). *Am J Cardiol* 37:163 1976
  - 54 Klein M S, Coleman R E, Weiss A N, and Roberts

suddenly changes from atrial fibrillation to a sinus rhythm. Another tragedy from thromboembolism is the occasional occurrence of a devastating cerebral embolus in a patient who previously has had minimal symptoms from his mitral stenosis. Other common secondary changes are the development of pulmonary hypertension and tricuspid insufficiency.

The insidious slowly progressive nature of mitral valve disease invites continued medical therapy for the disease is primarily one of restriction of blood flow from the lungs so the left ventricle is not injured as occurs in mitral insufficiency or aortic valve disease. Hence by restricting physical activity and using diuretics patients may be treated medically for decades with reasonably good results. Ultimately however operation is usually required and also there is the ever present risk of thromboembolism. Unfortunately when operation is done prosthetic replacement is often necessary and atrial fibrillation often remains permanent.

#### **Operative techniques**

Open mitral commissurotomy at New York University has been routinely performed for several years using cardiopulmonary bypass using a standard technique with hemodilution, a bubble oxygenator and roller pumps. At a temperature of 25° C the aorta is intermittently clamped for 10 to 15 minutes intermittently unclamping the aorta with a large catheter vent in the root of the aorta to remove air after which the heart is defibrillated. This combination of intermittent unclamping and periodically defibrillating the heart has proved a very reliable technique for resulting cardiac complications have been negligible.

The tricuspid valve is routinely explored for insufficiency and when found corrected with a posterior leaflet annuloplasty in over 95 per cent of cases. The only exception is when true organic tricuspid valve disease is present.

The atrial appendage is carefully checked for thrombi, after which the incision is routinely closed from within with a continuous suture of Prolene. This is placed carefully with superficial bites to avoid injury to the adjacent circumflex coronary artery but has now been routinely done for over 4 to 5 years with only one instance of injury to the coronary artery occurring several years ago clearly from a technical error. It is surprising that

the technique of routine closure of the atrial appendage has not been widely adopted because of the well known problem of continued fibrillation in patients who have been fibrillating for a long time before operation is performed. In patients with a prosthetic valve replacement who remain in atrial fibrillation it of course is impossible to tell whether a subsequent episode of thromboembolism originated from the prosthetic valve or the fibrillating appendage.

Commissurotomy is performed by incising the fused commissures throughout their length stopping a short distance from the annulus usually only a few millimeters where the commissure ends. The commissurotomy is never carried completely to the annulus because a true commissure does not extend to the annulus as small accessory leaflets are present. The change from a thickened fused commissure to a thin one is a clear technical guide to indicate where the commissurotomy should be stopped.

In some patients commissurotomy is extremely simple while in others it is complex and difficult. Several techniques of exposure are crucial including cardiac arrest, a wide atrial incision and proper positioning of a malleable retractor to expose the mitral valve. Shifting the retractor as little as 2 cm. can greatly impair visualization.

The key guide in commissurotomy is being certain that the mobilized leaflets are attached to the underlying chordae. In some instances the chordae actually lie close to the under surface of the fused commissure and can be readily severed if the anatomy is not clearly visualized. The triple right angle technique emphasized by Mullin and associates<sup>2</sup> in 1974 has been routinely used and remains very valuable.

A more difficult technical problem which well illustrates the advantage of open over closed commissurotomy is found when chordae are fused and often shortened to approximate the fused commissure to the underlying papillary muscle. By carefully separating the commissure the underlying papillary muscle can be split and also the fused chordae separated obtaining a functional valve that would normally be replaced and certainly could not be adequately opened with a closed digital commissurotomy.

A technique that has greatly facilitated radical commissurotomy is the ability to detect mitral insufficiency at the time of operation and correct this with sutures or an annuloplasty if necessary.

# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

## A plea for early, open mitral commissurotomy

Frank C. Spencer MD

New York N Y

The concept developed in this short report is that technical advances with open mitral commissurotomy have progressed to where operation should be considered at a much earlier stage than is usually done at present. Specifically, available data<sup>1,5</sup> support the concept that open mitral commissurotomy should be almost routinely performed in a patient with few symptoms, a small gradient at catheterization and a calculated cross sectional valve area decrease to 1.3 to 1.5 square centimeters. It is similar to the recommendation of operation for a healthy asymptomatic 16 year old child with a large atrial septal defect and a pulmonary blood flow three times normal. Even though the child can usually function well for years without operation, the long term course is well known, so early operation is routinely advised.

A major concept underlying the importance of early operation is that a radical valvulotomy, not only eliminating the gradient but opening the valve as much as possible without producing insufficiency, may prevent progressive fibrosis from turbulent flow of blood which in turn will require prosthetic replacement rather than reconstruction when operation becomes necessary months or years later.

### Etiologic considerations

Two different pathologic processes are probably significant with rheumatic mitral valve disease. Virtually everyone agrees that the basic cause is rheumatic fever. What is not readily recognized is the concept proposed by Selzer and Cohn<sup>6</sup> that the continuing turbulent flow of blood, produced by the orifice malformed by the

rheumatic inflammatory process, leads to progressive fibrosis, thickening and calcification at an unpredictable rate. This may occur within a few years or may extend over three or four decades. It is not unusual for a patient in the sixth decade with a distinct rheumatic history in the late 'teens' or early 'twenties' to remain minimally symptomatic for the next 20 to 30 years but eventually progress to severe calcific mitral stenosis requiring prosthetic replacement. The process is similar to that now well recognized in congenital aortic stenosis with a bicuspid valve where patients may not develop calcific aortic stenosis until the sixth or seventh decade of life. Hopefully, early radical commissurotomy that decreases the turbulent flow of blood may prevent these late changes.

### Pathologic processes

Three basic processes occur with mitral valve disease. The simplest and most common is fusion of the commissures from the rheumatic inflammation. A more advanced injury is fusion and shortening of the underlying chordae often depressing the fused commissures down to the underlying papillary muscle. The third most severe injury is thickening and subsequent calcification of the valve leaflets which could result from the mitral inflammatory process but probably more commonly results from long standing turbulent flow like that with aortic valvular disease. When this occurs repair is virtually impossible.

Serious secondary changes are the inevitable development of left atrial hypertrophy soon followed by atrial fibrillation and the ever present risk of thromboembolism from thrombi accumulating in the fibrillating appendage. On a few occasions the author has found 3 to 4 mm thrombi at operation lying freely in the atrial appendage like peas in a pod. This may be the mechanism of acute embolism in the patient who

From the Department of Surgery, New York University Hospital, Bellevue Medical Center, 550 First Ave., New York, N.Y.

Received for publication Jan. 30, 1978.

Reprint requests: Frank C. Spencer, MD, Department of Surgery, New York University Hospital, Bellevue Medical Center, 550 First Ave., New York, N.Y. 10016.

## Increase of WBC CRP, and BSR following cardiac pacemaker implant

The author has noted transient increase of serum C reactive protein (CRP) white blood corpuscles (WBC) and blood sedimentation rate (BSR) following pacemaker implant. In 25 consecutive patients WBC CRP and BSR were frequently checked following cardiac pacemaker implant. The average age of these 25 patients was 53.8 years. Pacemaker units employed in this series were all CPI Maxith (models 401 and 301). All 25 cases that had received endocardial pacing showed an uneventful postoperative course without any fever or infection. Examinations of WBC CRP and BSR were done preoperatively on the first postoperative day (the day after surgery) and on the second the third the fifth, and the seventh postoperative days.

WBC showed a wide variety among cases. Preoperative WBC was expressed as 100 in each case and postoperative WBC was shown by means of an index number compared to the preoperative number. The marked increase of WBC was noted on the first postoperative day in all cases. The highest index was 227 the lowest 107. The average index was  $155 \pm 30$  ( $\pm 30$  was the standard deviation) on the first day. It was  $146 \pm 24$  on the second day and  $122 \pm 22$  on the third day. The index returned to the preoperative level on the fifth day showing  $104 \pm 17$ . It was  $96 \pm 9$  on the seventh day when some cases showed less than preoperative indices.

CRP was classified into the following groups in our laboratory:  $- + - 1 + 2 + 3 + 4 + 5 +$  and  $6 +$ . Both  $-$  and  $+$  were included in  $-$  (negative) group. In order to calculate average value of CRP  $-$  (negative) was expressed as "zero". CRP The average was  $1.9 +$  on the first  $3.4 +$  on the second  $3.1 +$  on the third  $1.7 +$  on the fifth and  $0.8 +$  on the seventh postoperative days. The highest rise was noted on the second day. On the seventh day 2 out of 25 cases got to negative or  $1 +$ .

BSR was measured by the Westergren method. Only the rate of the 60 minute interval was compared. Preoperative BSR was  $11 \pm 6$  mm ( $\pm 6$  was the standard deviation) on the average. On the first day it was  $16 \pm 10$  mm. It was  $13 \pm 12$  mm on the second day  $32 \pm 17$  mm on the third,  $26 \pm 19$

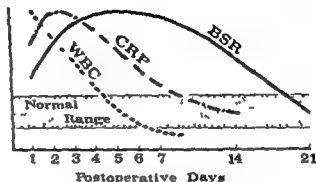


Fig 1 Diagrammatic representation of WBC CRP and BSR showing postoperative rise and fall following pacemaker implantation. See text for explanation.

mm on the fifth day and  $33 \pm 18$  mm on the seventh. BSR showed a gradual increase following implant, reaching its maximum level on about the fifth postoperative day and being normalized in three weeks.

WBC is increased and decreased more promptly than CRP. The latter precedes the rise in BSR. The schema of these three parameters was drawn in Fig 1. WBC shows the fastest CRP the middle and BSR the slowest changes. Physicians have to remember these usual changes of WBC CRP and BSR following pacemaker implant in order to differentiate these changes from any acute infection, acute myocardial infarction, rheumatic fever, tuberculosis, etc.

As various artificial organs are increasingly implanted in the human body, more attention should be paid to changes in these parameters.

Masavoshi Yokoyama MD  
Associate Professor  
The Heart Institute  
Tokyo Women's Medical College  
Shinjuku Tokyo Japan

## Significance of nausea and vomiting during acute myocardial infarction\*

Early diagnosis of myocardial infarction is crucial but often difficult. Diagnostic importance of extracardiac manifestations has been emphasized in the past. In patients with acute

myocardial infarction, the symptom complex of nausea and vomiting has previously been referred to as non-specific or as a result of analgesic therapy.\*

This study was undertaken prospectively to evaluate the diagnostic and prognostic significance of nausea and vomiting in patients with acute myocardial infarction.

Supplemented by Grant (GR 2 ES 75) from Essex County Heart Association, affiliate of the American Heart Association.

This is done by retrograde insertion of a catheter with multiple perforations across the aortic valve, as described by Mulholland and colleagues.

Rarely debridement of calcium may be feasible for annuloplasty may be combined with commissurotomy.

Clearly techniques of mitral reconstruction rather than replacement are still evolving, evidenced by the work of Carpentier in Paris, Reed at New York University and Rumel at Salt Lake City. An important concept is that reconstruction is probably far more feasible and durable than has been considered possible in the past.

This aggressive, radical commissurotomy has now been performed at New York University for several years. The technique has a very low mortality rate in the range of 1 to 3 per cent. Recurrent stenosis has not been seen in any patient operated on by the author in the last ten years and the only late complication observed has been the development of insufficiency in patients in whom fibrosis and distortion of the leaflets were already present. Undoubtedly the result of continued turbulent flow of blood and fibrotic contraction. Recurrent emboli have also been virtually unknown since the policy of routinely closing the atrial appendage was adopted several years ago.

It is well recognized that this concept may never be proved statistically because of the long progressive course of mitral valve disease often extending over three to five decades, and also because the relative frequency of reconstruction versus replacement will vary not only with the experience and attitude of the surgeon but with the type of valve pathology seen by him. For example, a surgeon experienced and enthusiastic about reconstruction might perform commissurotomy in 95 per cent of cases if patients are referred for operation with relatively early disease while a similar surgeon might find it necessary to perform replacement in over 30 per cent of cases if patients are referred only with far advanced disease and extensive calcification.

#### REFERENCES

1. Gerami S, Mesmer B, J. Hallman G I and Cooley D A. Open mitral commissurotomy. *J Thorac Cardiovasc Surg* 62:366 1971.
2. Mullin M J, Engelman R M, Isom O W, Boyd A D, Glassman E and Spencer F C. Experience with open mitral commissurotomy in 100 consecutive patients. *Surgery* 76:974 1974.
3. Reed G E. The repair of mitral regurgitation. An 11 year experience. *Am J Cardiol* 31:496 1973.
4. Carpentier A. Material presented at the Annual Meeting of the American College of Surgeons, Dallas, Texas, October 1977.
5. Rumel W R. Personal communication.
6. Selzer A and Cohn K F. Natural history of mitral stenosis. A review. *Circulation* 45:878 1972.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 765, Schenectady, N.Y. 12301, 518-374-4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

tors emphasized the precipitability of nephritogenic antibody observing that immunologically responsive rabbits developed chronic glomerulitis provided only that the daily antigen injection was sufficient to remove circulating antibody and maintain temporary antigen excess. Similarly in SLE the human analogue of chronic serum sickness controversy exists concerning the role of antibody precipitability in the pathogenesis of renal disease. Using the technique of counterimmunoelectrophoresis to examine SLE sera a high degree of correlation was demonstrated between renal involvement and the absence of precipitating DNA antibody with 64 to 75 per cent of patients with lupus nephritis having no demonstrable precipitates. The measurement of spontaneously precipitating and total DNA antibody by radioimmunoassay however has led to the conflicting observation that all lupus patients with clinically determined mild or severe nephritis had precipitating DNA antibody.

We sought to clarify this issue by designing a study which differed from previous investigations in the following ways: (1) All patients with nephritis were biopsied and the tissue obtained thoroughly characterized by light immunofluorescent and electron microscopy; (2) the biopsy and serum specimens from all patients were obtained prior to instituting corticosteroids or immunosuppressants thereby removing therapy induced alterations of antibody quantity or character; and (3) precipitating antibody from the test serum was measured both by radioimmunoassay and counter immunoelectrophoresis. Our results (summarized in Table I) demonstrated that patients with diffuse proliferative nephritis or active lupus without renal involvement evidenced a vigorous native DNA antibody response with a significant amount being precipitating in character. In contrast patients with membranous nephropathy were unique in synthesizing significantly less total native DNA antibody essentially all of which was non precipitating.

If non precipitating antibodies to DNA are less efficient at complement fixation and possibly immune elimination of antigen membranous lupus nephropathy may be a consequence of the persistence in the circulation of complexes of DNA with non precipitating antibody and the infiltration of the glomerular capillary wall (GBM) with such complexes leading to membranous thickening without significant inflammation. Alternatively since free DNA is frequently demonstrable in the circulation of SLE patients and the GBM has a high affinity for such DNA membranous lupus nephropathy may result from local formation at the GBM of complexes involving DNA and non precipitating DNA antibody. In summary the formation of complexes with native DNA and non precipitating DNA antibody either in the circulation or *in situ* may well be essential to the development of membranous lupus nephropathy.

Peter S Friend MD  
Department of Medicine  
University of Minnesota Hospitals  
Minneapolis Minn 55455

## REFERENCES

1. Pincus T., Haberkern R. and Christian C. L. Experimental chronic glomerulitis. *J Exp Med* 127:819 1968
2. Wilson C. B. and Dixon F. J. Quantitation of acute and

**Table I. Summary of native DNA antibody profiles of patients with diffuse proliferative nephritis (PRO) active lupus without renal disease (NO) and membranous nephropathy (MEM)**

|   | PRO           | NO             | MEM    |
|---|---------------|----------------|--------|
| Mean total DNA antibody (%)                                   | 96.2          | 69.9           | 26.6   |
| Mean precipitating DNA antibody (%)                           | 62.9          | 52.4           | < 1    |
| Ratio†  | 0.66          | 0.67           | 0.04   |
| Range of total DNA binding capacities (ng/ml)                 | > 2.53-26.624 | > 2.355-13.107 | 49-627 |
| Number of patients positive in counter immunoelectrophoresis‡ | 4/4           | 4/4            | 1/5    |

Radioimmunoassay results expressed as percentage of <sup>125</sup>I DNA bound by anti body

†Ratio = precipitating/total DNA antibody

‡Precipitation reaction of test serum with 20.5 or 1.25 mg DNA/mL

- chronic serum sickness in the rabbit. *J Exp Med* 134:76, 1971
3. Santerson C. Williams W. D. and Cameron J. S. Precipitating antibodies in systemic lupus. *Lancet* i 677 1974
4. Johnson G. D. Edmond J. P., and Holborow E. J. Precipitating antibody to DNA detected by two-stage electroimmunodiffusion study in SLE and in rheumatoid arthritis. *Lancet* i 883 1973
5. Johnson G. D., Edmonds J. P., and Holborow E. J. Precipitating antibodies in systemic lupus. *Lancet* i 760 1974
6. Gerstwin M. E. and Steinberg A. D. Qualitative characteristics of anti DNA antibodies in lupus nephritis. *Arthritis Rheum* 17:947 1974
7. Friend P. S. Kim Y. Michael A. F. and Donsdio J. V. Pathogenesis of membranous nephropathy in systemic lupus erythematosus: possible role of nonprecipitating DNA antibody. *Br Med J* 1:93 1977
8. Tamoto K. Nakamura T., and Koyama J. Non precipitating guinea pig antibodies produced by administration of excessive doses of ovalbumin. *Immunology* 26:455 1974
9. Margu R. and Bonaghi R. Purification and properties of non precipitating rabbit antibodies. *Immunology* 22:567 1972
10. Tan E. M. Schur P. H., Carr R. I. and Hunkel H. G. Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus. *J Clin Invest* 45:1737 1966
11. Hoffer D. Agnello V. Winchester R. and Hunkel H. G. The occurrence of single-stranded DNA in the serum of patients with systemic lupus erythematosus and other diseases. *J Clin Invest* 52:198 1973
12. Iru, S. Lambert P. and Mescher P. A. In vitro demonstration of a particular affinity of glomerular basement membrane and collagen for DNA. *J Exp Med* 144:428 1976



**Table 1 Patients with acute infarction**

|                   | All        | Anterior   | Inferior |
|-------------------|------------|------------|----------|
| 1 Number          | 62         | 33         | 29       |
| 2 Males           | 47         | 28         | 19       |
| 3 Females         | 15         | 5          | 10       |
| 4 Age (years)     | 60.1 ± 1.5 | 61.2 ± 2.1 | 59 ± 2.3 |
| 5 Nausea/vomiting | 29         | 9          | 20*      |
| 6 Bradycardia     | 18         | 4          | 14       |

P vs anterior wall infarct < 0.01 0.001

Sixty two patients with a diagnosis of acute myocardial infarction admitted to the Coronary Care Unit of St Joseph's Hospital in Paterson New Jersey were interviewed for the presence of nausea and/or vomiting by one of the authors before the administration of analgesics. None had previous gastrointestinal disorders, diabetes, hypertension or cerebral dysfunction or a heavy meal preceding the present episode. Subsequent follow up was carried out during the hospitalization period especially with regard to continuous nausea or vomiting, drugs administered, arrhythmias and enzyme changes.

Of the 62 patients, 33 (53 per cent) had anterior and 29 (47 per cent) had inferior wall myocardial infarction. The diagnosis of acute myocardial infarction was confirmed by characteristic chest pain, serial electrocardiographic and cardiac enzyme changes.

While only nine out of 33 (27 per cent) patients with anterior wall myocardial infarction complained of nausea and vomiting, this symptom was present in 20 of 29 (69 per cent) patients with inferior wall myocardial infarction (chi square = 9.2,  $P < 0.003$ ) (Table 1).

Nausea and vomiting in inferior wall but not anterior wall myocardial infarction was associated with bradycardias ( $P < 0.05$ ). In contrast, patients complaining of nausea and vomiting with anterior wall but not with inferior wall were younger ( $53 \pm 1$  vs  $64 \pm 2$  years) and had higher enzyme values on admission (SGOT 449 ± 58 vs 289 ± 34, LDH 815 ± 87 vs 357 ± 69) (all  $P$ s < 0.05). The higher enzymes in this group probably reflected heart failure which was present

in all nine cases of AMI with nausea and vomiting ( $P < 0.05$ ) and CPK values were similar.

The four subgroups differed insignificantly with regard to pain, characteristic blood pressure, tachyarrhythmias and hospital stay.

These data indicate that the nausea and vomiting are an important symptom complex in the diagnosis of myocardial infarction. These symptoms could be used as guides in the anatomic location of infarct as they are more frequently associated with inferior wall than with anterior wall myocardial infarction (69 vs 27 per cent).

Cardiogenic vomiting has been attributed to cardiogenic shock because of association of sweating and pallor. In the present study in anterior wall myocardial infarction one of the patients who had nausea and vomiting had cardiogenic shock. Conversely, of the three patients with anterior wall myocardial infarction who developed cardiogenic shock, none had nausea or vomiting.

Thus the mechanism of this symptom complex appears to be based on the vaso-vagal reflex. This is borne out by the fact that the bradycardia which results from the reflex vagal activity like nausea and vomiting is more frequently noted in patients with inferior than with anterior wall myocardial infarction.

S Sultan Ahmed M.D. FRCP(C) FACC  
R C Gupta M.D.  
Russell R Brancato M.D.  
Department of Medicine  
St Joseph's Hospital  
and Department of Medicine  
CUMCJ—New Jersey Medical School  
Newark N.J. 07107

## REFERENCES

- Hochberg H M. Characteristics and significance of prodromes of coronary care unit patients. *Chest* 59 10 1971.
- Douthwaite A H. Intractable hiccupping in acute myocardial infarction. *Br Med J* 2 709 1971.
- Ikram II, Orchard R T and Read S E. Intractable hiccupping in acute myocardial infarction. *Br Med J* 2 504 1971.
- Noble B G. Extracardiac manifestations of early acute myocardial infarction. *Med Trial Tech Q* 15 71 1969.

## A unique antibody response associated with the development of membranous nephropathy in systemic lupus erythematosus

The importance of qualitatively different populations of antibody in determining the inflammatory potential of circulating immune complexes in animal models of chronic serum sickness and human systemic lupus erythematosus (SLE) is well known. The precise role of antibody precipitability however is unclear since numerous investigations have yielded seemingly conflicting results.

In rabbits chronically immunized with bovine serum albumin

one group of investigators noted that in contrast to the rapidly eliminated immune complexes formed by animals without nephritis, rabbits with nephritis formed significant amounts of non-precipitating antibody. The lesser avidity for the reticulo-endothelial system of the small complexes formed by non-precipitating antibody was thought to lead to slower clearance and nephrotoxicity. In the same animal model of chronic serum sickness, however, another group of investiga-

tors emphasized the precipitability of nephritogenic antibody observing that immunologically responsive rabbits developed chronic glomerulitis provided only that the daily antigen injection was sufficient to remove circulating antibody and maintain temporary antigen excess. Similarly in SLE the human analogue of chronic serum sickness controversy exists concerning the role of antibody precipitability in the pathogenesis of renal disease. Using the technique of counterimmunoelectrophoresis to examine SLE sera a high degree of correlation was demonstrated between renal involvement and the absence of precipitating DNA antibody with 75 per cent of patients with lupus nephritis having no demonstrable precipitins. The measurement of spontaneously precipitating and total DNA antibody by radioimmunoassay however has led to the conflicting observation that all lupus patients with clinically determined mild or severe nephritis had precipitating DNA antibody.

We sought to clarify this issue by designing a study which differed from previous investigations in the following ways: (1) All patients with nephritis were biopsied and the tissue obtained thoroughly characterized by light immunofluorescent and electron microscopy. (2) The biopsy and serum specimens from all patients were obtained prior to instituting corticosteroids or immunosuppressants thereby removing therapy induced alterations of antibody quantity or character and (3) precipitating antibody from the test serum was measured both by radioimmunoassay and counter immunoelectrophoresis. Our results (summarized in Table I) demonstrated that patients with diffuse proliferative nephritis or active lupus without renal involvement evidenced a vigorous native DNA antibody response with a significant amount being precipitating in character. In contrast patients with membranous nephropathy were unique in synthesizing significantly less total native DNA antibody essentially all of which was non precipitating.

If non precipitating antibodies to DNA are less efficient at complement fixation and possibly immune elimination of antigen membranous lupus nephropathy may be a consequence of the persistence in the circulation of complexes of DNA with non precipitating antibody and the infiltration of the glomerular capillary wall (GBM) with such complexes leading to membranous thickening without significant inflammation. Alternatively since free DNA is frequently demonstrable in the circulation of SLE patients and the GBM has a high affinity for such DNA membranous lupus nephropathy may result from local formation at the GBM of complexes involving DNA and non precipitating DNA antibody. In summary the formation of complexes with native DNA and non precipitating DNA antibody either in the circulation or in situ may well be essential to the development of membranous lupus nephropathy.

Peter S Friend MD  
Department of Medicine  
University of Minnesota Hospitals  
Minneapolis Minn 55455

## REFERENCES

1. Pincus T, Haberkern R and Christian C I. Experimental chronic glomerulitis, *J Exp Med* 127:819 1968.
2. Wilson C M and Dixon F J. Quantitation of acute and

**Table I** Summary of native DNA antibody profiles of patients with diffuse proliferative nephritis (PRO) active lupus without renal disease (NO) and membranous nephropathy (MEM)

|   | PRO          | NO           | MEM    |
|---|--------------|--------------|--------|
| Mean total DNA antibody (%)                                   | 96.2         | 69.9         | 26.6   |
| Mean precipitating DNA antibody (%)                           | 67.9         | 57.4         | < 1    |
| Ratio†  | 0.66         | 0.66         | 0.04   |
| Range of total DNA binding capacities (ng/ml)                 | > 9537-26624 | > 1355-13107 | 49-627 |
| Number of patients positive in counter immunoelectrophoresis‡ | 4/4          | 4/4          | 1/5    |

Radioimmunoassay results expressed as a percentage of <sup>125</sup>I DNA bound by antibody

†Ratio = precip (ng)/total DNA antibody

‡Precipitin reaction of test serum with 20.5 or 1.25 mg. DNA/ml.

- chronic serum sickness in the rabbit *J Exp Med* 134:76 1971
3. Sanderson C, Williams H D and Cameron J S. Precipitating antibodies in systemic lupus. *Lancet* : 677 1974
4. Johnson G D, Edmond J P and Holborow E J. Precipitating antibody to DNA detected by two-stage electroimmunodiffusion study in SLE and in rheumatoid arthritis. *Lancet* : 883 1973
5. Johnson G D, Edmonds J P and Holborow E J. Precipitating antibodies in systemic lupus, *Lancet* : 750 1974
6. Gershwin M E and Steinberg A D. Qualitative characteristics of anti DNA antibodies in lupus nephritis, *Arthritis Rheum* 17:947 1974
7. Friend P S, Kim Y, Michael A F and Donadio J V. Pathogenesis of membranous nephropathy in systemic lupus erythematosus: possible role of nonprecipitating DNA antibody. *Br Med J* 1:25 1977
8. Tamoto K, Nakamura T and Koyama J. Non precipitating guinea pig antibodies produced by administration of excessive doses of ovalbumin. *Immunology* 26:455 1974
9. Margm, R and Binaghi, H. Purification and properties of non precipitating rabbit antibodies. *Immunology* 22:557 1972
10. Tan E M, Schur P H, Carr R I and Kunkel H G. Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus. *J Clin Invest* 45:1739 1966
11. Koffler D, Agnello V, Winchester R and Kunkel H G. The occurrence of single stranded DNA in the serum of patients with systemic lupus erythematosus and other diseases. *J Clin Invest* 52:198 1973
12. Iru S, Lambert P and Miescher P A. In vitro demonstration of a particular affinity of glomerular basement membrane and collagen for DNA. *J Exp Med* 144:428 1976

## Of the sham operation

Because of the tremendous number of coronary artery bypass operations performed each day and the astronomical costs even by present standards and the good results reported even when the shunts are closed there is a great need for evaluation of this operation by sham bypass surgery (operations in which the heart is exposed and the pericardium opened but no actual shunts done) as well as evaluation of the effects of the mere existence of surgery. All sham operations must be performed as a double blind therapeutic test procedure. Before a drug or medical type of therapeutic agent is approved by the FDA for general use, even for less serious and less hazardous illnesses the agent must be evaluated by double blind or sham studies. Why are there not the same

strict standards of testing for a surgical therapeutic agent? There is a definite need for sham coronary bypass operations to evaluate coronary bypass surgery. Of course there is an ethical problem to be considered.

George E. Burch, M.D.  
Tulane University School of Medicine  
and Charity Hospital  
New Orleans, La.

### REFERENCE

1. DiLuzio V, Roy P R, and Sowton E. Angina in patients with occluded aorto coronary vein grafts. *Br Heart J* 36:139, 1974.

## Menstruation and heart disease

To The Editor

I was intrigued by Seely's editorial (March 1976 issue) which suggests that menstruation may play a role in protecting women against heart disease—surely one of the few beneficial things that have been written about menstruation in the course of medical history and appropriate to current feminist concepts. He then alludes to a possible beneficial role of venesection that mainstay of medieval medicine.

One of the ways to check this theory would be to look at cardiovascular mortality rates in blood donors and I would be interested to know if anyone has any information on this. Demonstration of a beneficial effect of blood donation would be a welcome aid to sorely pressed blood banks around the world.

Michael Goodyear  
Department of Haematology  
Prince Henry's Hospital  
St Kilda Road  
Melbourne 3004  
Australia

## REFERENCE

- 1 Seely S Possible reasons for the comparatively high resistance of women to heart disease *AM HEART J* 91 775 1976.

## Blood donors and coronary disease

To The Editor

In reply to Dr Goodyear's letter may I say first of all that the appropriateness of my views to current feminist concepts as well as their possible resemblance of medieval practices are purely accidental.

I have not realized that I made medical history by being the first to say a kind word about menstruation. I certainly do not know of anyone having done so in the past, but Shakespeare might have had the same idea when pointing out that every cloud had a silver lining. He did not make his meaning entirely clear but then he used only six words as against 3 000 in my article.

As far as I know no literature is available on differences in cardiovascular mortality rates between blood donors and a suitable control group. Before I called attention to the possibility that it could be hemorrhages not estrogens that may have a prophylactic effect on atherogenesis, it does not seem to have occurred to anyone to carry out such a survey. After the publication of the article the possibility seems to have generated some interest. Investigation concerning mortality rates of blood donors particularly male blood donors, has already been suggested twice to me in correspondence related in the article notably by Dr H. Moors the University of Manchester and by a doctor in Hospital Cantonal Geneva whose name I could not decipher. I cannot carry out such an investigation myself but I would be glad if someone did. There are two alternatives such a survey could

take. It would be possible to select a group of male blood donors, preferably in the over forty age groups, whose future medical history would be followed. Alternatively it would be possible to select a group who were blood donors let us say 20 years ago and attempt to trace their history in the intervening years. Obviously the disadvantage of the first method is the long time it would take to obtain statistically significant results, and of the second the great difficulties and expense involved in tracing the fate of the selected group.

A considerable amount of research has been done on the allied subject of differential reactivity of women with early and late onset of menopause the early onset being due either to natural causes or ovariectomy. A recent leading article in the *British Medical Journal* gave a somewhat sketchy survey of the past literature dealing with the subject, as well as some editorial opinions, the latter hotly debated in subsequent editorial correspondence. The most interesting of the quoted references is a Swedish study comparing the menstrual histories of women with known coronary heart disease with a randomly selected control group. According to this 76 per cent of the women admitted to hospital with myocardial infarction had passed through the menopause before the age of 50 in comparison with 48 per cent of the controls. In women however the resumption of menstrual hemorrhages is inseparable from hormonal changes, so that it is impossible to know with certainty which one of these factors affects reactivity to coronary heart disease. This is the reason why an investigation on male blood donors would be important.

I might perhaps add that I wrote two subsequent papers to the article under consideration. One is published in the November 1977 issue of *Medical Hypotheses* the other on "The atherogenic effect of stilbestrol" was recently submitted to *AMERICAN HEART JOURNAL*.

Stephen Seely B Sc  
3 Truro Drive  
Sale Cheshire M33 5DF  
England

## REFERENCES

- 1 Leading article Coronary heart disease and the menopause *Br Med J* 1 862, 1377
- 2 Elkeles A Letter to the Editor (in answer to article of Ref 1) *Br Med J* 1 1215 1977
- 3 Bye P Letter to the Editor (in answer to article of Ref 1) *Br Med J* 1 1215 1977
- 4 Bengtsson C Ischaemic heart disease in women *Acta Med Scand Suppl* 549 19 7
- 5 Seely S Surfactants and atherogenesis *Med Hypotheses* 3 259 1977

## Overdiagnosis of left anterior hemiblock

To The Editor

In the October 1977 issue of *THIS JOURNAL* Dr G E Burch cautions against overdiagnosing left anterior hemiblock (LAH). This caution is justified but Rosenbaum in his

monograph discussed the differences between this form of fascicular block and horizontal heart with clockwise rotation LVH etc His criteria included an axis of  $-60$  degrees—but at least  $-45$  degrees In Dr Burch's example the axis is not that far to the left Other possibilities of incorrectly diagnosing LAH include inferior infarction with large Q waves aberrant conduction due to pre excitation and others In the case of LVH the question still has to be solved if an axis of  $-60$  degrees in LVH could not be due to fascicular block caused perhaps by stretching of the septal fibers

Of course the diagnosis of LAH per se does not imply a grave prognosis and in an asymptomatic patient a pacemaker is certainly not indicated

Otto Neurath M D  
Professor of Medicine  
New Jersey Medical School  
New Jersey College of Medicine  
and Dentistry  
Newark New Jersey

# Retrograde Wenckebach phenomenon in ventricular tachycardia

To the Editor

The purpose of this letter is to present a rather rare ventriculoatrial conduction during ventricular tachycardia documented by intracavitary (IC) recordings

In a 69 year old man with resistant ventricular tachycardia antiarrhythmic drugs and four electric shocks had been without result Therefore a bipolar electrode catheter was inserted into the right heart and short periods of ventricular overdriving succeeded in converting the heart to sinus rhythm

The IC electrograms recorded during arrhythmia from the

right atrium show a retrograde ventriculoatrial conduction with a progressive prolongation of the ventriculoatrial interval followed by a nonconducted ventricular beat thus a retrograde Wenckebach phenomenon as shown on the two IC electrograms recorded simultaneously

S Cotor  
C Georgescu  
P Colea  
First Medical Clinic  
(Dir Prof dr C Duden)  
Institut Medico Farm  
4300-Tirgu Mures  
Romania

## REFERENCES

- 1 Goldreyer H N and Biggar J T Ventriculo atrial conduction in man *Circulation* 41 935 1970
- 2 Kustin A D Retrograde conduction to the atria in ventricular tachycardia *Circulation* 24 236 1961
- 3 Nicolai P Delage M Medvedovski L Arnoux M and Jouve A Conduction auriculaire retrograde permanente en cours de tachycardie ventriculaire *Arch Mal Coeur* 63 1057 1970
- 4 Cotor S and Dragulescu S A simple intracavitary bedside method for estimation of the PR interval *Cor Vasa* 17 96 1975
- 5 Waldo A L Kongrad E Kupersmith J Levine O R Bowman F O and Hoffman H F Ventricular paired pacing to control rapid ventricular heart rate following open heart surgery *Circulation* 53 176 1976
- 6 Damato A N Lau E H and Bobb G A Studies on ventriculo atrial conduction and the re entry phenomenon *Circulation* 41 423 1970
- 7 Puech P Grolleau R Latour H Cabasson J and Marin J Diagnostic des tachycardies ventriculaires avec conduction retrograde par la stimulation endocavitare *Arch Mal Coeur* 64 789 1971

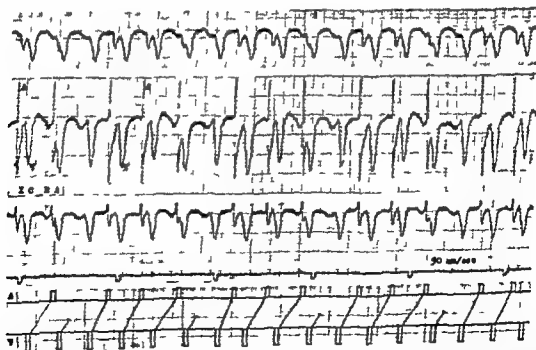


Fig 1 A simultaneous recording of three intracavitary electrograms from the right atrium (ICRA) In the bottom panel is a diagrammatic presentation Paper speed 50 mm per second A = Atrial activity V = ventricular activity

## Book reviews

**Coronary Artery Surgery: A Critical Review** By Thomas A. Preston M.D. New York 1977 Raven Press 270 pages Price \$12.50

The title of this book summarizes very well its contents. The author has reviewed papers published supporting and attacking bypass surgery for coronary artery disease. This of course is interesting to the readers of this book but those who have followed the literature closely and without bias know that this approach will not decide the value of coronary artery bypass surgery. As the author states in conclusion on page 257 coronary artery surgery is neither proven nor disproven as a beneficial mode of therapy. And Dr. Preston is correct but what justifies this book? Readers who have not followed the literature closely or who have only read or accepted one point of view will find both the pro and con points of view reviewed. The historical chapter should interest young surgeons and cardiologists who did not know Claude Beck, or do not know Vinberg and others who pioneered the surgical management of coronary artery disease. The chapters on placebo effects, psychological factors and financial incentives deal with well known factors in therapeutics to clinicians and need discussion.

It is interesting that Preston writes about courageous editorialists who indicated the need to evaluate operations. This requires no courage. It is only an obvious demand for reliable and objective data indicating definite value for any therapeutic agent before it is employed or recommended to less informed physicians. There certainly is a need to know what is right.

In summary this is an interesting book but the reader will find no answer as to the value of bypass surgery nor unfortunately even a recommendation to withhold surgical therapy until a definite answer as to its value is obtained. This would suggest that Preston is of the opinion that bypass surgery is an acceptable procedure even without proof of its value whereas the criteria of the FDA requires established therapeutic value of medicinal agents prior to recommendation of their general use in medicine. In fact the FDA disapproved Lasinol since its effectiveness has not been established or proven. Why use different standards or different criteria for coronary bypass surgery?

Therefore after an extensive review of the literature this book does not answer the question: Is coronary bypass surgery useful for ischemic heart disease and if this is not known, should it continue to be performed at the present tremendous rate? And, what should doctors advise their patients to do at present? Undergo an expensive operation of unproven therapeutic value?

**Physiology of the Heart and Circulation** By Robert C. Little Chicago 1977 Year Book Medical Publishers Inc 334 pages

This paperback book on physiology of the heart and circulation contains an excellent brief review of the physiology of cardiac and circulatory function. The author has presented principles which are generally accepted. The relationship of function to structure and disease is clearly and briefly presented. The 14 chapters include discussions of fluid movement, cardiac structure, electrophysiology and electrocardiography, cardiac dynamics, cardiac work, hemodynamic phenomena, structure of the blood vessels, and venous and

pulmonary circulations. The illustrations are well chosen and the bibliography carefully selected. This book should interest all physicians who treat diseases of the heart and circulation as well as medical students. It should be included among books recommended to medical students and housestaff.

**Nuclear Cardiology: Principles and Methods** Edited by Aldo Scrafino, Albert J. Gibson and William M. Smoak, New York and London 1977 Plenum Medical Book Company 249 pages Price \$22.50

Nuclear medicine is a rapidly expanding field in medicine. The application to clinical cardiovascular states is likewise increasing rapidly. However, like all developing methods and their applications, the interpretation of data offers difficulties. The physician must learn to know when the method is useful in his practice. With critical review of this book, readers will find the use of nucleides to have limited supplemental value in the practice of cardiology. For example, is it the patient's best interest during the early phases of a fresh infarct of the myocardium to be transferred to a nuclear medicine laboratory to attempt to delineate the area of infarction when it can be done at the bedside with a properly recorded electrocardiogram? And what about the cost? Regardless of these and other aspects of the problems related to nuclear cardiology, the cardiologist at least must be well informed of presently active interests in cardiology. This book describes the field very well. The book is divided into five parts to which others knowledgeable in nuclear cardiology contribute. The five parts are concerned with fundamental principles, shunt detection in congenital heart disease, evaluation of myocardial blood flow, evaluation of ventricular function and the role of radioimmunoassay in cardiology. These subjects are reviewed very well and from the viewpoint of clinical cardiology rather than laboratory research. Those involved in nuclear cardiology, as well as the practicing physician, will find the book useful. This reviewer hopes that readers will not consider this type of study superior to others nor assume that the methods are fully evaluated and developed. Nevertheless, this is a timely book which includes aspects of an important subject into a single volume for the convenience of many cardiologists and internists.

**Advances in Cardiology** volume 20 *Future Directions in the Management of Cardiac Disease* Edited by John H. H. Vogel, New York 1977 S. Karger AG 143 pages

This publication summarizes the Seventh Conference on Cardiovascular Diseases held in Aspen, Colorado during January 1976. The eleven papers included in this book review primarily coronary artery disease and left ventricular function. Prevention and maintenance of good cardiac health are the main points of emphasis. Bypass surgery and medical care for ischemic heart disease constitute a prominent part of the discussions. The reader will find this to be a mature review of important problems in cardiology. The discussions of prevention of coronary heart diseases, coronary artery dysfunction, integrated medical-surgical treatment of pre-infarction syndrome and the results of repair of congenital heart defects are among the subjects discussed. This volume of *Advances in Cardiology* is another good one and certainly worth owning.

## Books received

**Disorders of Hemostasis in Surgery** Edited by Witold J Rudowski Hanover New Hampshire 1977 The University Press of New England 456 pages Price \$17.50

**Infective Endocarditis** Edited by Edward L Kaplan M D and Angelo V Taranta M D Dallas 1977 American Heart Association 86 pages Price \$6.00

**Medical and Health Information Directory** Edited by Anthony T Kruzas Detroit 1977 Gale Research Company 664 pages Price \$48.00

**Intensive Coronary Care A Manual for Nurses** third edition By Lawrence E Meltzer M D Rose Pinneo R N and J Roderick Mitchell Bowie Maryland 1977 The Charles Press Publishers 274 pages Price \$20.88

**Exercise in Cardiovascular Health and Disease** Edited by Ezra A Amsterdam M D Jack H Wilmore Ph D and Anthony N DeManno M D New York 1977 Yorke Medical Books 376 pages Price \$33.00

## Announcements

### Medex 78

Medex 78 the Fourth International Exhibition for Medical Electronics and Bioengineering will take place in the halls of the Swiss Industries Fair in Basle Switzerland from June 6 to 10 1978 In conjunction with the exhibition a technical meeting on computer tomography (CAT) will be held on June 6 and 7 under the chairmanship of Professor M Anliker and Dr P Rueggsegger from the Institute of Biomedical Technology of the Federal Institute of Technology and the University of Zurich

For further information regarding the exhibition and meeting please contact The Secretariat Medex 78 c/o Swiss Industries Fair P O Box CH 4021 Basle Switzerland Telephone 061/26 20 20 Telex collect 62685

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published Authors will be consulted when possible regarding republication of their material

### Fifth European Congress of Anaesthesiology

The Fifth European Congress of Anaesthesiology will be held in Paris on September 4 through 9 1978 There will be 70 sessions in seven lecture halls Simultaneous translations will be provided in English French German and Spanish Topics covered will be hemodynamic variations in anesthesia in obstetric anesthesia and analgesia anesthesia for vascular surgery pediatric anesthesia anesthesia for emergency surgery anesthesia for cardiac surgery and sodium nitroprus-

sode in clinical practice—anesthesia and resuscitation Also presented will be anesthesia and resuscitation problems in neurosurgery emergency surgery traumatologic surgery radiology E N T surgery ophthalmological surgery digestive surgery urological surgery surgery in the aged thoracic surgery gynecological and obstetrical surgery orthopedic surgery problems due to intoxication and pharmacology and clinical use of new muscle relaxants

For registration information and registration requests for free papers and films please contact Congress Anesthesiologie—P M V B P 246 92205 Neuilly sur Seine France

### Society of Nuclear Medicine meeting

The Third Annual Western Regional Meeting of the Society of Nuclear Medicine will be held at the Hotel Vancouver in Vancouver B C Canada on October 13 14 15 1978 The Northern California Southern California Pacific Northwest and Hawaii Chapters are sponsoring this meeting The program will consist of invited papers contributed papers registry review courses for technologists and refresher courses for physicians The Scientific Program Committee welcomes the submission of abstracts of original contributions in nuclear medicine for the Third Annual Western Regional Meeting Physicians Scientists and Technologists members and nonmembers are invited to participate The Program will be structured to permit the presentation of papers from all areas of interest in the specialty of Nuclear Medicine Abstracts submitted by technologists are encouraged and will be presented at the scientific program Abstracts for the scientific program will be printed in the program booklet and will be available to all registrants at the meeting

Please address all correspondence regarding the submission of abstracts and the exhibiting of commercial companies to Justine J Lynch Administrative Coordinator P O Box 40279 San Francisco CA 94140 Telephone (415) 647-6722 or 647 5909

## Editorial

### Inferior vena caval interruption in the prevention of fatal pulmonary embolism

A M N Gardner DM MCh FRCS

Newton Abbot Devon England

When medical measures to control pulmonary embolism fail or are contraindicated mechanistic approaches can save lives

The surgery entailed is sufficiently safe for prophylactic application in certain cases for example when mandatory operations have to be performed on patients with thromboembolic disease particularly when anticoagulant therapy is contraindicated

Trousseau was the first to suggest the interposition of a barrier between the thrombus and the large veins in cases of pulmonary embolism This was in 1868 twelve years after Virchow's first account of the pathological features of the condition Only now a century later is it possible to evaluate the various physical methods of preventing fatal pulmonary embolism

#### Pathological and hemodynamic considerations

The clinician's picture of pulmonary embolism shows only the tip of the iceberg since small clinically undetectable emboli are the rule rather than the exception in ill and elderly patients<sup>1,2</sup> Indeed it might be better for them to speculate on which patients have not had emboli rather than the reverse Small emboli are usually (satisfactorily) lysed in the lungs but some remain as the strands and bands described by Virchow (1860) in the pulmonary arteries Such strands may arise from the lysis resistant platelet elements (Zahn's

lines) in the thrombus They are also commonly seen in the long veins after thrombosis where they may arrest small emboli arising more peripherally and so cause recurrent local thromboses It takes a large pulmonary embolus to produce symptoms and only emboli of 7.5 mm or more in diameter<sup>1</sup> are likely to be lethal although the size of the patient and any degree of pre-existing blockage to the pulmonary arterial tree are relevant

Most lethal emboli arise from the leg or pelvic veins but emboli from the subclavian veins particularly after parenteral feeding can be fatal Two such cases were recognized only at autopsy when it was realized that the emboli in the lungs were too large to have traversed the site of the partial vena caval occlusion Judging from the literature right atrial and hepatic vein origins of emboli are much less common

In patients suffering from thromboembolism peripheral thromboses are usually multiple and their propagation is often extremely rapid being measured in hours rather than in days This process may be exacerbated by peripheral phlebography For these reasons the concept of total phlebography of legs and pelvis followed by appropriate local surgery to lock in the clot<sup>3</sup> is unsound furthermore this technique seldom adequately demonstrates the internal iliac veins which are the source of about 10 per cent of fatal emboli

The inferior vena cava is the final common path of the great majority of dangerous emboli and is thus the optimal area for their surgical arrest Local narrowing by surgery to prevent the

From the T. B. y Hospital, T. B. y England

Received for publication July 26, 1977

Reprint requests: Dr. A. M. N. Gardner, T. B. y Hospital, T. B. y Devon, TQ 7AA, England



onward passage of dangerous sized emboli has obvious advantages over complete ligation though of course the subsequent arrest of any large embolus will make the partial occlusion complete. Caval recanalization is the exception rather than the rule and is usually incomplete.

Criteria therefore for a satisfactory method of partial caval occlusion are first that it should reliably arrest emboli of a lethal size (7.5 mm) in diameter, secondly that it should not tend to become blocked by the unnecessary arrest of common insignificant small emboli, and thirdly that the narrowed area should have the largest possible cross section to allow free flow of blood.

Fig 1 illustrates the various methods of partial caval occlusion. Intraluminal filters and plications have the disadvantage that they arrest saddle fashion the common small clinically insignificant emboli, and moreover they soon distort and allow the passage of lethal sized emboli. Foreign material such as filters introduced into the lumen of the inferior vena cava become covered with a pseudo neointima that may proliferate greatly like vegetations on a heart valve. A comparative study of plications, filters and smooth external clips performed in a series of patients with inoperable abdominal neoplasms and so at a special risk from thromboembolism, showed clearly that the clips were superior. Not only were they highly effective, but they more commonly remained patent than other methods of partial occlusion.<sup>3</sup>

External clips of various designs have been used to narrow the lumen of the cava unlike intraluminal devices their application does not encourage primary thrombosis.<sup>2,4</sup> Serrated clips<sup>10,11</sup> have been popular, but they produce multiple discrete channels that have a smaller total cross sectional area of lumen than that of smooth clips. They are also likely to arrest small emboli saddle wise on the 'pillars' between the channels, these considerations together with the extra difficulty and potential danger of application suggest that they should be superseded by smooth clips whose safety and effectiveness is now well established.

The ideal smooth clip should be designed for oblique placement low on the cava to give maximal cross sectional area to the narrowed part.<sup>4</sup>

Such clips are obtainable from F. J. Payne and Son, Mill Lane, Osney Oxford.

In people of average build a 5.5 mm gap has proved effective. In large men the gap has been widened to 6.0 mm and in small women it has been narrowed to 5.0 mm and in one case of paradoxical embolism with normal pulmonary pressures, a 4.0 mm gap was used in such cases caval ligation might be wiser if pulmonary pressure is raised. The wall of the vena cava is 0.5 mm thick so in all cases the true lumen is 1.0 mm smaller than the gap in the clip.

Partial caval ligation with or without beads<sup>12,13</sup> is simple (see Fig 1), but produces an undesirably small lumen. Complete vena caval ligation is mandatory in cases of septic embolism, in cases where dangerous embolism continues after partial occlusion, and when pulmonary hypertension increases after such an operation. Ligation in ill patients particularly those with cardiovascular disorders, carries a high mortality rate (10 to 50 per cent) from fluid sequestration in legs and pelvis. The efficiency of the collateral venous circulation varies considerably from patient to patient, it is most efficient in women with intact ovarian veins, most of whom develop only minor transient leg swelling after lower caval ligation. The optimal site for both partial and complete caval occlusion is as low as possible in the inferior vena cava. The collateral circulation here is more efficient than in the upper part of the post renal cava. Anatomical studies of cavae blocked by emboli at various levels have shown clearly that the most important parts of the collateral circulation are the inflowing lumbar vessels which are seen at the main point of embolus occlusion (or even below it), to drain into the upper cava through channels in the thrombus. The same studies likewise showed a negligible danger of embolism from propagated thrombus above such a low occlusion.

Complete ligation of the inferior vena cava inevitably results in a dilation of the collaterals that is absent in a satisfactory partial occlusion. Embolism via these dilated collaterals is well documented although passage of lethal sized emboli is rare, perhaps because the mouths of dilated collaterals seldom themselves dilate to more than 3 or 4 mm.<sup>14</sup> Ligation certainly cannot be counted on permanently to protect against microembolism but experience shows that it is effective in the rare case where clinical episodes of pulmonary embolism occur after partial caval occlusion.

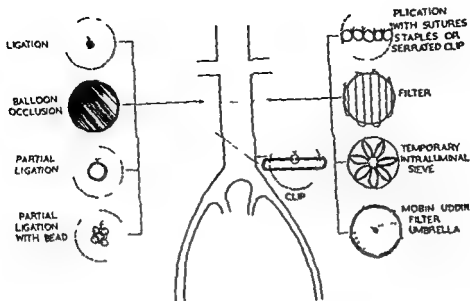


Fig 1 Diagrammatic representation of the various methods and devices used in the inferior vena cava to arrest lethal sized emboli (7 mm diameter or larger)

Patients who are suffering uncontrolled pulmonary embolism but are unfit for operation may be tided over the danger period by the transvenous insertion of various devices

Safe simplest and effective is the Eichelter sieve<sup>3</sup> quickly fabricated from easily available plastic tubing and introduced from the groin. Partial caval occlusion by clip is advisable after a few days at the time of its removal

Simple permanent but completely occlusive is the balloon device of Hunter and associates<sup>4</sup>. The umbrella filter of Mobin Uddin also permanent is more complex sometimes dangerous may become dislodged and has very small channels prone to blockage by small emboli

#### Results of partial caval occlusion by clip

Twelve years experience indicates that clips provide continuing and probably permanent protection against fatal embolism. The price of such protection is an increased incidence of peripheral venous thrombosis in the postoperative period with persistent new leg swelling in about one in five of the patients so treated. Usually this swelling is easily controlled. Two out of 50 patients followed up for a minimum of five years suffered venous claudication the most severely affected being a senior physician who claudicated on hills but enjoys a normal active social life. Most clips retain patency but the majority of the patients with bilateral swelling

had caval blocks whereas only one out of five patients with unilateral swelling had such a block.

Caval blocks are almost always the result of impacted emboli. The incidence of these emboli and the causative peripheral thrombophlebitis are certainly increased by partial caval occlusion. The reason for this has been obscure the clips used in this series with a gap measuring 5.5 mm by 2.5 cm produced no measurable pressure differential. Significant wave damping was noted however and since inferior vena caval blood flow is markedly pulsatile (personal observation with a 2 MHz ultrasonic Doppler haematocrytograph) it seems likely that pulsatile flow is an important factor in maintaining venous patency in the femoro iliac regions and that the smoothing out of this flow, favors thrombosis.

#### Mortality

In reasonably skilled hands partial caval occlusion is no more dangerous than other intra-abdominal operations. Reported mortality figures are often misleading because they include numbers of desperately ill patients often subjects of pulmonary embolectomy.

In the author's personal series of 517 mainly elective partial caval occlusions there were four deaths attributable to the surgery. The only intraoperative death was in a patient who suffered a massive pulmonary embolism and a

few hours later a perforated duodenal ulcer. Two later deaths followed septic complications of peripheral thrombophlebitis, one other patient died when an embolus passed through a faulty clip which had widened to give an 8 mm gap.

There is no doubt that in appropriate cases the application of a caval clip can be life saving. Moreover it is a relatively simple and speedy technique, soon learned and well within the scope of any District General Hospital. To date it has not gained wide popularity possibly because of confusion with caval ligation, or because its dangers have been exaggerated.

But viewed in the light of its proven high effectiveness in protecting against pulmonary embolism, it surely deserves a recognized place in our armamentarium against pulmonary embolism, and where anticoagulants fail or are inappropriate it finds its clearest indications.

#### REFERENCES

- Gardner A M N, Askew A R, Harse H R, Wilmshurst C C and Turner M J. Partial occlusion of the inferior vena cava in the prevention of fatal pulmonary embolism. *Surg Gynecol Obstet* 138:17, 1974.
- Trousseau A. *Lectures on Clinical Medicine* vol V, p 302. translation by J H Cormack of the 3rd edition of 1868. London 1872. New Sydenham Society.
- Gardner A M N. Surgery in the prevention of fatal pulmonary embolism. *Ann R Coll Surg Engl* 47:260, 1970.
- Morrell M T and Dunnill M S. The post mortem incidence of pulmonary embolism in a hospital population. *Br J Surg* 55:347, 1968.
- Freeman D G, Suyemoto J and Wessler S. Frequency of pulmonary thromboembolism in man. *N Engl J Med* 272:1278, 1965.
- Virehow R L K. *Cellular Pathology* 7th ed. New York 1860. pp 230-245.
- Lewis I. *Modern trends in cardiac surgery* edited by H R S. Harley. London 1960. Butterworth & Co Ltd. p 56.
- Browne N L, Thomas M L, Solan M J and Young A E. Prevention of recurrent pulmonary embolism. *Br Med J* 3:382, 1969.
- Wray C H, Callahan T, Dixon J H, Price T B and Moretz W H. Thrombosis at the site of interruption of the vena cava: a consideration in prophylactic treatment of pulmonary embolism. *Am Surg* 41:714, 1975.
- DeWeese M S and Hunter D C Jr. A vena cava filter for the prevention of pulmonary embolism: a five year clinical experience. *Arch Surg* 86:852, 1963.
- Miles R M. Prevention of pulmonary embolism by the use of a plastic vena caval clip. *Ann Surg* 163:197, 1966.
- Murley R A. A self releasing inferior vena caval clip. (Letter) *Lancet* 1:790, 1961.
- Mores M and Antebi E. A simple method for ligation of the inferior vena cava. *Surg Gynecol Obstet* 125:367, 1967.
- Crane C. Venous interruption for pulmonary embolism: present status. *Prog Cardiovasc Dis* 17:329, 1975.
- Eschelter P and Schenk W G Jr. Prophylaxis of pulmonary embolism: a new experimental approach with initial results. *Arch Surg* 97:348, 1968.
- Hunter J A, Sessions R and Tetasmick J. Therapeutic balloon occlusion of the inferior vena cava. *JAMA* 234:1034, 1975.
- Askew A R and Gardner A M N. Long term follow up of partial caval occlusion by clip. (Submitted for publication 1977).

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement, signed by each author: 'The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published. Authors will be consulted when possible regarding republication of their material.'

### Non specific aorto arteritis in Singapore with special reference to hypertension

P C Teoh MB MMed MRCP MRACP FCCP\*

L K A Tan MB DMRD FRCP\*\*

B L Chua MB FRACP FACC\*\*

T C Chao MB DMJ DPath FCLM FRCPA

FCAP\*\*

J A Tambiah MB FRACP\*\*

PH Feng MB FRCP(G)\*\*

Singapore Singapore

Aorto arteritis has recently emerged as a distinct disease entity with involvement of aorta and its major branches by a non specific inflammation of unknown etiology. Because of its protean manifestations it was formerly known as Takayasu's disease, pulseless disease, brachial arteritis, arteritis of aorta in young women, young female arteritis, aortic arch syndrome, reversed coarctation syndrome, or occlusion of supra aortic trunks and many other exotic names. Each of these names emphasized a different mode of clinical presentation of this disease and some of them stressed the predominance of female patients affected by this disease. Since any segment of the aorta and any of its major branches might be affected, Schrire and Asherson in 1964 coined the term arteritis of the aorta and its major branches. Recently Sen proposed that it should be most appropriately and conveniently named non specific aorto

arteritis. 'Though the distribution of this disease is worldwide and does occur occasionally in the Western world, it is more prevalent in Japan, India and Southeast Asia. In Singapore, Dana Raj and Wong first reported two cases in 1959 and subsequently another nine cases of aorto arteritis presenting with hypertension as a result of renal arteries involvement.' The purpose of this paper is to describe a series of 48 cases seen by us in Singapore to emphasize the protean nature of the disease and to point out the frequency of hypertension as a manifestation.

#### Clinical material

The criteria for the diagnosis of non specific aorto arteritis are vascular bruits over the neck, abdomen and inter scapular area, unequal or absent neck or limb pulses, especially in children and young adults and the absence of evidence of other disorders like syphilis, systemic lupus erythematosus and polyarteritis. Radiological examination is essential for the diagnosis. Thoracic and/or abdominal aortography was employed to confirm the diagnosis in 38 out of the 48 patients included in this series. In the remaining 10 patients where no aortography was done, the diagnosis was confirmed in seven of them by postmortem examination.

The age, sex and race distribution are shown in Table I. The disease is more common in children and young adults and the majority of them (37 patients) were below 30 years of age. The youngest was 7 years old and the oldest was 48 years old with a mean age of 23 years. As in other series, the disease affected predominantly the

From the University Department of Medicine, Singapore General Hospital, Singapore.

Received published in Oct 25 1976

Accepted for publication March 16 1977

Reprint request to P C Teoh, University Department of Medicine, Singapore General Hospital, Singapore 3.

Senior Lecturer, University Department of Medicine, Singapore General Hospital.

Consultant Radiologist, Department of Radiology, Singapore General Hospital.

Associate Professor, University Department of Medicine, Singapore General Hospital.

Senior Pathologist, Department of Pathology, Singapore General Hospital.

Consultant Physician, Department of Medicine, Singapore General Hospital.

Consultant Physician, Department of Medicine, Tan Tock Seng Hospital.

few hours later a perforated duodenal ulcer. Two later deaths followed septic complications of peripheral thrombophlebitis, one other patient died when an embolus passed through a faulty clip which had widened to give an 8 mm gap.

There is no doubt that in appropriate cases the application of a caval clip can be life saving. Moreover it is a relatively simple and speedy technique, soon learned and well within the scope of any District General Hospital. To date it has not gained wide popularity, possibly because of confusion with caval ligation, or because its dangers have been exaggerated.

But viewed in the light of its proven high effectiveness in protecting against pulmonary embolism, it surely deserves a recognized place in our armamentarium against pulmonary embolism, and where anticoagulants fail or are inappropriate it finds its clearest indications.

#### REFERENCES

- Gardner A M N, Askew A R, Harve H R, Wilmshurst C C and Turner M J. Partial occlusion of the inferior vena cava in the prevention of fatal pulmonary embolism. *Surg Gynecol Obstet* 138:17, 1974.
- Trousseau A. *Lectures on Clinical Medicine* vol V p 302, translation by J R Cormack of the 3rd edition of 1868. London 1872. New Sydenham Society.
- Gardner A M N. Surgery in the prevention of fatal pulmonary embolism. *Ann R Coll Surg Engl* 47:260, 1970.
- Morrell M T, and Dunnill M S. The post mortem incidence of pulmonary embolism in a hospital population. *Br J Surg* 55:347, 1968.
- Freeman D G, Suyemoto J and Wessler S. Frequency of pulmonary thromboembolism in man. *N Engl J Med* 272:1278, 1965.
- Varchow R L. K. *Cellular Pathology* 7th ed. New York 1960 pp 230-245.
- Lewis I. *Modern trends in cardiac surgery*, edited by H R S Harley. London 1960. Butterworth & Co Ltd., p 56.
- Browse N L, Thomas M L, Solan M J and Young A E. Prevention of recurrent pulmonary embolism. *Br Med J* 3:382, 1969.
- Wray C H, Callahan T, Dixon J B, Price T H and Moretz W H. Thrombosis at the site of interruption of the vena cava: a consideration in prophylactic treatment of pulmonary embolism. *Am Surg* 41:714, 1975.
- DeWeese M H and Hunter D C Jr. A vena cava filter for the prevention of pulmonary embolism: A five year clinical experience. *Arch Surg* 86:852, 1963.
- Miles R M. Prevention of pulmonary embolism by the use of a plastic vena caval clip. *Ann Surg* 163:199, 1966.
- Murley R. A self releasing inferior vena caval clip. (*Letter*) *Lancet* 1:790, 1961.
- Moses M and Antebi E. A simple method for ligation of the inferior vena cava. *Surg Gynecol Obstet* 125:369, 1967.
- Crane C. Venous interruption for pulmonary embolism: present status. *Progr Cardiovasc Dis* 17:329, 1975.
- Eichelter P and Schenk W G Jr. Prophylaxis of pulmonary embolism: A new experimental approach with initial results. *Arch Surg* 87:348, 1968.
- Hunter J A, Sessions R and Petasnick J. Therapeutic balloon occlusion of the inferior vena cava. *JAMA* 234:1034, 1975.
- Askew A R and Gardner A M N. Long term follow up of partial caval occlusion by clip. (Submitted for publication 1977).

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement, signed by each author: "The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published." Authors will be consulted, when possible regarding republication of their material.



Fig 1 Constriction of aorta at the lower descending artery

them had  $\square$  gallop rhythm. Though aortic incompetence was noted in four patients it was severe and hemodynamically significant in only one patient. Mitral incompetence was encountered in two patients, most probably secondary to congestive heart failure and presumably functional in nature. Ischemic changes with ST segment depression and flattened or inverted T waves were found in the electrocardiograms (ECGs) of nine patients, and coronary artery occlusion or narrowing in four patients was found during autopsy. But no frank myocardial infarction was detected in any of our patients.

**Pulse abnormalities and vascular bruits.** Pulse abnormalities are characteristic of aorto arteritis because of frequent involvement of major branches of the aorta. Weak or absent pulses were found to occur in 30 patients. They were more common in the upper limbs and neck than in the lower limbs. Left side pulses were more frequently affected than those of the right. Lower limb pulses were affected in 11 patients in our series; only one presented with intermittent claudication and gangrene of the leg. There were some mild nutritional changes in others. Vascular bruit was another characteristic feature of aorto-



Fig 2 Dilatation of the ascending aorta and the innominate artery with obliteration of both subclavian arteries

arteritis and was heard in 29 patients. Abdominal bruits were the commonest and occurred in 22 patients. Bruits over the neck were heard in 16 patients and over the chest in five others. In 13 patients the bruits were heard at more than one site, indicating the diffuseness of the lesions in aorto arteritis. Difference in pulses and the presence of bruits over one or more arteries were the most useful signs in the diagnosis of aorto arteritis. Unless examination for differential pulse and vascular bruits becomes part of the routine assessment of the patients, examples of this disease would undoubtedly be missed or overlooked.

**Angiographic studies.** Though the diagnosis of this disease can be often reached by careful clinical examination, angiographic studies are essential to confirm the diagnosis and to outline clearly the type and extent of the lesion. Abdominal aortograms were performed in 30 patients

Table I Age, sex and race distribution

| Age (years) | Male | Female | Chinese | Malay | Indian | Total |
|-------------|------|--------|---------|-------|--------|-------|
| 0-9         | 0    | 1      | 1       | 0     | 0      | 1     |
| 10-19       | 6    | 12     | 16      | 2     | 0      | 18    |
| 20-29       | 6    | 12     | 13      | 2     | 3      | 18    |
| 30-39       | 3    | 6      | 7       | 1     | 1      | 9     |
| 40-49       | 0    | 2      | 1       | 1     | 0      | 2     |
| Total       | 15   | 33     | 38      | 6     | 4      | 48    |

Table II Chief complaints

| Symptom                   | No. of cases |
|---------------------------|--------------|
| Dyspnea                   | 9            |
| Headache                  | 9            |
| Unequal pulses            | 8            |
| Giddiness                 | 5            |
| Palpitation               | 5            |
| Hemiparesis               | 5            |
| Chest pain                | 4            |
| Ankle edema               | 4            |
| Hemoptysis                | 3            |
| Syncope                   | 3            |
| Fits                      | 2            |
| Fever                     | 2            |
| Blurred vision            | 2            |
| Intermittent claudication | 1            |
| Painful nodules           | 1            |
| Ptoxis                    | 1            |
| Abdominal pain            | 1            |
| Sudden death              | 1            |

young females. A total of 33 females were affected compared with 15 males in this series, giving a female to male ratio of 2.2 to 1. Among them there were 38 Chinese, 6 Malays, and 4 Indians. It did not appear that any of the above races was affected more frequently than the others as the ratio corresponded quite closely to the composition of the various races in Singapore.

Table II showed the chief complaints of our patients. They were many and varied. Chief complaints related to cardiac involvement were dyspnea, palpitation, chest pain and ankle edema. Complaints related to cerebral circulatory impairment were headache, giddiness, blurred vision, syncopal attacks and fits. Complaints related to circulatory disturbance of the extremities were unequal or absent pulses and intermittent claudication.

Table III revealed the major modes of presentation among the 48 patients studied. Thirty

Table III Major modes of presentation

|                 |    |
|-----------------|----|
| Hypertension    | 33 |
| Unequal pulses  | 30 |
| Vascular bruits | 29 |
| Cardiac failure | 14 |
| Hemiparesis     | 5  |
| Aneurysms       | 4  |
| Optic atrophy   | 1  |

Table IV Signs of cardiac involvement

|                              |    |
|------------------------------|----|
| Cardiomegaly                 | 21 |
| Cardiac failure              | 14 |
| S <sub>3</sub> gallop rhythm | 11 |
| Aortic incompetence          | 4  |
| Mitral incompetence          | 2  |

three patients had hypertension. 30 had unequal or absent pulses. 29 patients developed vascular bruits at various sites. 14 patients were in cardiac failure. Five patients presented with hemiparesis and four were admitted with aneurysms and died of rupture or dissection. Optic atrophy was detected in one patient who complained of blurring of vision.

**Hypertension.** Hypertension was the commonest mode of presentations of aorto arteritis in this series of patients. It occurred in 33 patients. It was the predominant manifestation in 14 patients and it co-existed with other manifestations in the remaining 19 patients. The hypertension was mild (diastolic 90 to 104 mm Hg) in 12 patients, moderate (diastolic 105 to 114 mm Hg) in 15 patients, and severe (diastolic 115 mm Hg or higher) in six patients. One of them presented with hypertensive encephalopathy. Abdominal bruits were heard in 22 patients with hypertension and subsequent abdominal aortogram revealed stenosis or occlusion of renal arteries in 25 patients with hypertension. Two additional cases of renal artery stenosis were found on autopsy. Therefore hypertension was renovascular in origin in 27 patients. Two other patients were found to have coarctation of aorta to account for the hypertension whereas in the remaining four patients no obvious mechanism was found.

**Cardiac involvement.** The frequency of cardiac involvement in aorto arteritis in our series of patients was clearly shown in Table IV. In 21 patients there was clinical evidence of cardiomegaly. 14 of them developed cardiac failure and 11 of



Fig 1 Constriction of aorta at the lower descending artery

them had a gallop rhythm. Though aortic incompetence was noted in four patients it was severe and hemodynamically significant in only one patient. Mitral incompetence was encountered in two patients most probably secondary to congestive heart failure and presumably functional in nature. Ischemic changes with ST segment depression and flattened or inverted T waves were found in the electrocardiograms (ECGs) of nine patients and coronary artery occlusion or narrowing in four patients was found during autopsy. But no frank myocardial infarction was detected in any of our patients.

**Pulse abnormalities and vascular bruits.** Pulse abnormalities are characteristic of aorto arteritis because of frequent involvement of major branches of the aorta. Weak or absent pulses were found to occur in 30 patients. They were more common in the upper limbs and neck than in the lower limbs. Left side pulses were more frequently affected than those of the right. Lower limb pulses were affected in 11 patients in our series; only one presented with intermittent claudication and gangrene of the leg. There were some mild nutritional changes in others. Vascular bruit was another characteristic feature of aorto



Fig 2 Dilatation of the ascending aorta and the innominate artery with obliteration of both subclavian arteries

arteritis and was heard in 29 patients. Abdominal bruits were the commonest and occurred in 22 patients. Bruits over the neck were heard in 16 patients and over the chest in five others. In 13 patients the bruits were heard at more than one site indicating the diffuseness of the lesions in aorto arteritis. Difference in pulses and the presence of bruits over one or more arteries were the most useful signs in the diagnosis of aorto arteritis. Unless examination for differential pulse and vascular bruits becomes part of the routine assessment of the patients, examples of this disease would undoubtedly be missed or overlooked.

**Angiographic studies.** Though the diagnosis of this disease can be often reached by careful clinical examination, angiographic studies are essential to confirm the diagnosis and to outline clearly the type and extent of the lesion. Abdominal aortograms were performed in 30 patients





Fig 3 Aneurysms of the lower thoracic aorta and the abdominal aorta with an obliteration of right renal artery and superior mesenteric artery



Fig 4 Irregularities and dilations of the abdominal aorta with bilateral occlusion of the renal arteries near their orifices. Well developed collateral vessels fill the renal arteries later in the series. The superior mesenteric artery is seen just above the aortic kink as a large dilated vessel occluded soon after its origin

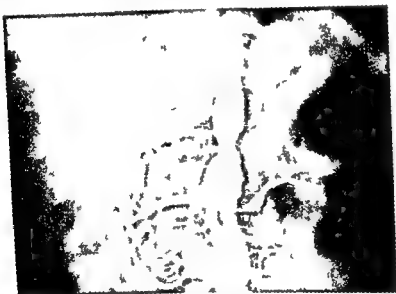
and arch and thoracic aortogram were done in 25 patients. The characteristic features of aorta in aorto arteritis were constriction (Fig 1), dilatation (Fig 2) aneurysm (Fig 3) irregularity (Fig 4) total occlusion (Fig 5), and lastly any of the above in combination (Fig 6). Table V shows the type, frequency and locations of aortic involvement. It is worth noting that the abdominal aorta was affected more frequently than the thoracic aorta. As for the thoracic aorta the descending portion bore the brunt of disease in 14 patients; the arch of the aorta was affected in five patients whereas the ascending aorta was least affected with lesions in only two patients. Table VI shows the frequency of involvement of the major arteries of the aorta by aorto arteritic process. The renal arteries (Fig 7) and the subclavian arteries (Fig 8) were the most commonly affected ones. Renal arteries were affected 39 times in 25 patients, out of whom 14 patients had bilateral renal artery involvement and the remaining 11

patients had either right or left renal artery disease.

**Laboratory investigation.** Mild anemia with hemoglobin of 9 to 12 Gm per cent was found in 16 patients, whereas moderate anemia with hemoglobin of less than 9 Gm per cent was found in three patients. Leucocytosis was noted in 12 patients whereas erythrocyte sedimentation rate (ESR) was elevated in 30 patients. In 12 of them the ESR was between 20 to 49 mm/hour in 15 of them it was between 50 to 100 mm/hour and only 3 patients had an ESR of more than 100 mm/hour. Antinuclear factor and direct Coombs test were negative and lupus erythematosus cells were absent in all the patients; however rheumatoid factors (RA) were positive in three patients. Kahn test and VDRL test for syphilis were negative in all except in two patients which finding we believed was incidental. None of them had an elevated serum cholesterol level. Blood urea and electrolytes were all



**Fig 5** Total occlusion of the abdominal aorta with extensive collateral formations



**Fig 6** Irregularities constrictions and dilatations of the abdominal aorta with stenosis and post stenotic dilatation of the left renal artery. There is also stenosis of the right renal artery origin clearly visible through the superior mesenteric artery

within normal limits. Electrocardiograms showed left ventricular hypertrophy in 21 patients and ischemic changes with ST segment depression and flattened or inverted T waves in nine patients. Chest radiograms showed cardiomegaly in 20 patients, pulmonary congestion in six patients, calcification of the aorta in eight patients and dilatation of the aorta in three patients.

**Progress.** Five patients were treated with oral corticosteroids and the response was equivocal. It did not appear to arrest the slow progress of the disease. Out of the 33 patients with hypertension, nephrectomy was done in three patients with favorable response in two. In both of them blood pressure became normal. The other 30 patients were treated medically with hypotensive agents such as chlorazothiazide, guanethidine, methyl

Table V Angiographic presentations

|                          | Abdominal aorta | Thoracic aorta |
|--------------------------|-----------------|----------------|
| Constriction             | 10              | 8              |
| Dilatation               | 8               | 9              |
| Aneurysm                 | 1               | 2              |
| Irregularity             | 7               | 3              |
| Combination of the above | 2               | 1              |
| Total occlusion          | 8               | 0              |

Table VI Involvement of major branches of aorta

|                     |    |
|---------------------|----|
| Innominate          | 5  |
| Carotids            | 13 |
| Subclavians         | 32 |
| Celiac              | 5  |
| Superior mesenteric | 9  |
| Renal               | 39 |

Table VII Causes of death

|                     |   |
|---------------------|---|
| Cardiac failure     | 4 |
| Dissecting aneurysm | 3 |
| Ruptured aneurysm   | 1 |
| Cerebral hemorrhage | 1 |
| Sudden death        | 1 |

dopa, debrisoquin sulfate and propranolol at conventional dosages. The control of blood pressure was satisfactory in 21 patients but poor in nine patients. The severity and the treatment of hypertension played an important part in the prognosis and the mortality of the patients with aorto arteritis. This was quite well shown by the fact that five patients died as a result of uncontrolled and severe hypertension, four of them from heart failure and one of them from cerebral hemorrhage (Table VII). Other causes of death included dissecting aneurysms, ruptured aneurysm and sudden death. Though the occurrence of aneurysms of the aorta and its main branches in aorto arteritis had increasingly been recognised, we were surprised to note that four out of 10 deaths were as a result of dissecting and ruptured aneurysms of the aorta. The diagnosis of non-specific aorto arteritis was confirmed on postmortem examination in all four cases. Therefore aneurysms should be regarded as an important manifestation of this disease entity, especially from the standpoint of prognosis. As rupture or dissection may occur surgical inter-

vention should be considered whenever possible. At the time of review there were 14 patients who were lost to follow up. Among the 24 patients who survived, 12 patients were still alive from 1 to 5 years later, seven were alive from 6 to 10 years later, and the remaining five were alive from 11 to 18 years later. The longest survival was 18 years. This indicated that the disease process was slow and chronic and the prognosis depended on the nature and the degree of involvement of the vessels and the severity of hypertension.

## Discussion

The occurrence of hypertension in aorto arteritis was first pointed out by Giffin in 1939 but it was considered unusual by Kalmansohn and Kalmansohn<sup>1</sup> in 1957. However, in 1961 Ask Upmark<sup>10</sup> showed that 29 out of 60 cases studied had increased blood pressure giving an incidence of 48 per cent. In Singapore it was Danaraj and co-workers<sup>2</sup> who first brought to our attention in 1959 that hypertension was not an uncommon manifestation of aorto arteritis.<sup>3-6</sup> This was later confirmed by Ooi and colleagues<sup>11</sup> in 1971 who showed that aorto arteritis contributed to 4 per cent of the 127 young hypertensive patients under study in Singapore. In our present series of 48 patients 33 patients suffered from hypertension giving an incidence of 69 per cent. This incidence was much higher than the 48 per cent reported by Ask Upmark<sup>10</sup> among Europeans and the 42 per cent reported by Schrire and Asherson among South Africans. However it was quite similar to the incidence of 64 per cent reported recently by workers in China.<sup>1</sup> It would therefore appear that hypertension was a far more common manifestation of aorto arteritis among the Asians and especially among the Chinese.

The commonest cause of hypertension in aorto arteritis in our series is renovascular with renal artery stenosis or occlusion occurring in 27 cases (85 per cent). Hypertension caused by coarctation of aorta was found in two patients only. In the remaining four patients with hypertension the mechanism was not obvious though it was possible that it might be due to the loss of elasticity of aorta as a result of diffuse aortic involvement as suggested by Ask Upmark.<sup>10</sup> Though hypertension is usually due to renal artery involvement one must bear in mind that the occlusion of the renal artery alone does not always insure that hypertension is on a renal



Fig 7 Stenosis of the left renal artery with long smooth constriction of the mid abdominal aorta



Fig 8 Absent left subclavian artery with dilatation of innominate artery. The right common carotid artery shows dilatations and irregularities and the left common carotid and the right subclavian artery are occluded as well

ischemic basis. Other factors like cerebral ischemia and involvement of baroreceptors in the affected aorta and/or carotid arteries must be considered as possible mechanisms of hypertension in such patients. The renal arteries were affected mainly at the ostia or the first parts hence differentiating them from other causes of renal artery stenosis like fibromuscular hyperplasia. The frequency of renal artery involvement is much greater than a comparable series reported by Ueda<sup>3</sup> in Japan who showed that out of 42 cases of aorto arteritis 12 patients had angiographic evidence of renal artery stenosis and two other patients revealed renal involvement on autopsy giving an incidence of 34 per cent. The frequency of renal artery involvement has only recently been appreciated even when the arch of aorta appears to bear the brunt of the disease. When the upper abdominal aorta is involved the renal arteries are almost universally affected and hypertension was a constant finding in most of our patients. Therefore renovascular hypertension should be regarded as a predominant feature

of this disease. The possibility of renovascular hypertension as a manifestation of aorto arteritis should always be considered in the diagnosis of hypertensive patients in Singapore especially if the patient is a young female since it greatly influences the prognosis of the disease.

#### Summary

Aorto arteritis has recently emerged as a distinct disease entity with involvement of aorta and its major branches by a non specific inflammation of unknown etiology. Though the distribution of this disease is worldwide it is more prevalent in Japan, India and South east Asia. This paper describes a series of 48 cases seen in Singapore and emphasizes the protean nature of this disease. Though modes of clinical presentation were many hypertension appeared to be the commonest as it occurred in 33 patients giving an

incidence of 69 per cent. This incidence was much higher than the 48 per cent reported among Europeans and 42 per cent reported among South Africans. It would therefore appear that hypertension was a far more common manifestation of aorto arteritis among Asians. The commonest cause of hypertension in aorto arteritis in this series was renovascular, with renal artery stenosis or occlusion occurring in 27 cases (85 per cent). The frequency of involvement of the renal artery is much greater than the 34 per cent reported by the Japanese. Therefore renovascular hypertension should be regarded as a predominant feature of aorto arteritis in Singapore.

We are grateful to Prof P K Wong Head University Department of Medicine and Prof O T Khoo Head University Department of Medicine Singapore General Hospital Prof C S Seah Head Department of Medicine Singapore General Hospital and Prof Y K Lee Head Department of Medicine Toa Payoh Hospital for their permission to study all the cases in their respective Units.

#### REFERENCES

- 1 Strachan R W. Pre-pulseless and pulseless Takayasu's arteritis. *Postgrad Med J* 42:464 1966
- 2 Schrire V and Asherson R A. Arteritis of the aorta and its major branches. *Q J Med* 33:439 1964
- 3 Sen P K. Non-specific aorto arteritis. A monograph based on a study of 101 cases, Bombay-New Delhi 1933. Tata McGraw Hill Co. p 13
- 4 Laude A and Rossi P. The value of total aortography in the diagnosis of Takayasu's Arteritis. *Radiology* 114:287 1975
- 5 Danaraj T J and Wong H O. Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension. *Circulation* 20:8-6 1959
- 6 Danaraj T J, Wong H O and Thomas M A. Primary arteritis of the aorta causing renal artery stenosis and hypertension. *Brit Heart J* 25:153 1963
- 7 Ueda H, Ohno K, Ito I et al. Two cases of aortitis syndrome with aneurysm formation. *Jpn Heart J* 9:88 1968
- 8 Giffin H M. Reversed coarctation and vasomotor gradient. Report of a cardiovascular anomaly with symptoms of brain tumour. *Proc Mayo Clin* 14:561 1939
- 9 Kalmansohn R B and Kalmansohn E W. Thrombotic obliteration of the branches of aortic arch. *Circulation* 15:237 1957
- 10 Ask Upmark E. On the pathogenesis of the hypertension in Takayasu's syndrome. *Acta Med Scand* 169:467 1961
- 11 Ooi H S, Chen B T M, Yu S F, Toh C C S and Khoo O T. Primary arteritis of the aorta as a cause of renovascular hypertension in Singapore. *Aust N Z J Med* 2:132 1971
- 12 Chinese Academy of Medical Sciences. Roentgenologic study of aorto arteritis. Analysis of angiography in 92 cases. *Chinese Med J* 1:42 1975
- 13 Ueda H. Renovascular hypertension as a manifestation of aortitis syndrome. *Jpn Heart J* 8:209 1967

# Myocardial infarction in the Black population of South Africa · Coronary arteriographic findings

Elliot Chesler MD FRCPE FACC\*  
Abdul S Mitha, MRCP (UK)  
E Kenneth Weir DM (Oxon) MRCP (UK)\*  
Rodney E Matisson MB ChB FCP (SA)  
Peter J Hitchcock, MB FCP (SA)

Natal, South Africa

Among the various racial groups of South Africa there exists a striking difference in the prevalence of myocardial infarction. The White population is afflicted to a degree which approximates that of the U.S.A. but in the age group between 25 to 44 years the incidence in the South African White may be the highest in the world. In contrast the Black population is almost immune to the disease.

Estimates of the prevalence of ischemic heart disease in the Black population have been derived from necropsy studies but predominantly from extensive electrocardiographic surveys.<sup>1-4</sup> There has however been no documentation of the coronary angiographic findings in Black patients who manifest clinical and electrocardiographic evidence of myocardial infarction. This paper reports our findings in 13 such patients who underwent this investigation. Our findings suggest that occlusive coronary atherosclerosis in the Black population may be even less common than suggested by previous electrocardiographic evidence.

From the Cardiac Unit, Wentworth Hospital, and the University of Natal, Durban, South Africa.

Supported by a grant from the Medical Research Council of South Africa.

Received for publication Mar 15 1977

Accepted for publication April 4 1977

Reprint requests Dr A S Mitha, Cardiac Unit, Wentworth Hospital, P B Jacobs, Natal, South Africa 4016.

Present address: Cardiovascular Division, Veterans Administration Hospital, 64th St & 48th Ave South, Minneapolis, Minn 55417

## Subjects and methods

This cardiac unit is the only referral service for coronary angiography in the Province of Natal. It therefore serves a population comprised of 1 132 697 Blacks 523 918 Whites 439 570 Asiatics and 68 091 Mulattoes.

Since 1968 we have performed a total of 800 coronary angiograms of which 13 were on Black and 787 on White patients. These Black patients form the subject of this report where we detail the findings at coronary arteriography and utilizing the admission figures to the general medical wards of our referring hospital comment on the prevalence of myocardial infarction.

All 13 patients were pure Black. All had experienced previous episodes of acute transmural myocardial infarction diagnosed on the basis of a characteristic clinical picture supported by unequivocal electrocardiographic findings of pathological Q waves and elevated ST segments. Serum transaminase (glutamic oxalacetic or glutamic pyruvic) or lactic dehydrogenase levels were raised in all patients. Serology for syphilis was always negative. In none was there evidence of dissecting aortic aneurysm, viral myocarditis or collagen disease. Serum cholesterol levels were measured in 11 patients and in seven a complete lipoprotein analysis was available. An enquiry into their socioeconomic status, dietary habits and family history was made.

Coronary arteriography was performed using the Judkins technique. Films were exposed at 64

**Table 1** Clinical, electrocardiographic, and coronary angiographic data on 13 Black patients with transmural myocardial infarction

| Patient no and age | Sex | Blood pressure | Cholesterol | ECC* location of infarct | No of coronary arteries affected | Mitral valve | Occupation         |
|--------------------|-----|----------------|-------------|--------------------------|----------------------------------|--------------|--------------------|
| 1 50               | M   | 140/80         | 168         | Inferior                 | 3                                | Normal       | Policeman          |
| 2 38               | M   | 100/70         | 228         | Anterior                 | 2                                | Normal       | Manual labourer    |
| 3 48               | M   | 100/70         | 288         | Anterior                 | 3                                | Normal       | Manual labourer    |
| 4 39               | M   | 110/80         | 264         | Inferior                 | 2                                | Normal       | Manual labourer    |
| 5 36               | M   | 140/90         | 201         | Inferior                 | 1                                | Normal       | Manual labourer    |
| 6 45               | M   | 140/90         | 262         | Inferior                 | 1                                | Normal       | Manual labourer    |
| 7 64               | M   | 110/70         | 166         | Anterior                 | 3                                | Normal       | Ex manual labourer |
| 8 46               | F   | 100/70         | ?           | Anterior                 | 2                                | Normal       | Housewife          |
| 9 35               | M   | 120/70         | ?           | Inferior                 | 2                                | Normal       | Policeman          |
| 10 40              | M   | 110/60         | 200         | Inferior                 | 1                                | Normal       | Manual labourer    |
| 11 32              | M   | 140/90         | 209         | Anterior                 | Nil                              | BMLS*        | Manual labourer    |
| 12 27              | M   | 120/80         | 201         | Anterior                 | Nil                              | BMLS         | Manual labourer    |
| 13 51              | M   | 130/70         | 222         | Anterior                 | Nil                              | Normal       | Manual labourer    |

BMLS = Billowing mitral leaflet syndrome ECC = electrocardiogram

frames per second using a 6 inch camera with an over framing lens. Left ventricular function was assessed angiographically in the right anterior oblique view following the injection of 50 cc of 70 per cent Urografin. The left ventricular end diastolic pressure and dp/dt were also available.

## Results

The material was divided into two groups on the basis of the coronary arteriographic findings (Table 1).

### Group A Angiographically abnormal coronary arteries (Cases 1 to 10)

**Age** The mean age was 44 ( $\pm 8.7$  SD) years.

**Sex** Nine were male and one was female.

**Occupation** Apart from two who were police men and the one female who was unemployed all were manual labourers.

**Blood pressure** This was normal in all patients.

**Serum cholesterol** This varied from 166 to 288 mg per cent mean 222 mg per cent.

**Left ventricular angiograms** There were always abnormal and revealed areas of hypokinesis, dyskinesia or aneurysm. In three the infarction was anterior and in three inferior. In two patients there was generalized hypokinesia or ischemic myopathy. The remaining two patients each had an anteroseptal aneurysm.

**Coronary arteriography** Significant lesions were considered to be present when 75 per cent of the lumen was obstructed. Three patients had

single vessel disease involving the right coronary artery. Five patients had diffuse disease in two vessels and the remaining three patients had triple vessel disease.

**Left ventricular end diastolic pressure** was elevated above 14 mm Hg in all but two patients.

### Group B Angiographically normal coronary arteries (Cases 11 to 13)

**Age** The mean age was 36.7 years.

**Sex** All were male.

**Occupation** All were manual laborers within the low income group.

**Blood pressure** This was within normal limits.

**Serum cholesterol** These were 209, 201, and 222 mg per cent.

**Left ventricular angiograms** Two of these patients had evidence of prolapse of the posterior leaflet of the mitral valve and left ventricular contractility was normal. The third patient with an anterior ventricular aneurysm did not have prolapse of the mitral valve.

**Coronary arteriography** Angiographically the coronary arteries were considered normal in all three patients.

**Left ventricular end diastolic pressure** This was normal apart from the patient with the aneurysm in whom it was 15 mm Hg.

**Prevalence of ischemic heart disease** An estimate of the clinical prevalence of ischemic heart disease among the Black population of Natal may

be made from statistics available from our referring hospital. During 1976 10 553 Black adult patients were admitted to the general medical wards. Among these there were five cases with unequivocal electrocardiographic and enzymatic evidence of transmural myocardial infarction providing a prevalence rate of only 0.05 per cent of medical admissions. However this figure should be treated with reserve since three of these five patients are included in our series and in one the coronary arteries were found to be angiographically normal. In the remaining 10 patients of our series studied before 1976 the coronary arteries were found to be normal in another two.

### Discussion

An accurate assessment of the prevalence of ischemic heart disease is difficult to obtain. National vital statistics are dependent upon accurate death certification and take no account of the prevalence in the living. A full electrocardiographic investigation is very helpful in establishing the diagnosis of ischemic heart disease provided the diagnostic criteria are rigid and an adequate sample of the population at risk is available for study. Numerous such studies have demonstrated the striking immunity of the South African Black population to ischemic heart disease but there has been some variation in the reported frequency in the clinical series (Table I). Thus Schwartz and colleagues<sup>1</sup> in an analysis of 50 cases among 417 000 medical admissions to Baragwanath Hospital for the period 1951 to 1961 determined a prevalence rate of 0.01 per cent. In comparison to control groups their 30 cases of myocardial infarction showed a marked predominance of males with a high incidence of hypertension, diabetes and obesity. In addition these subjects were engaged in the more skilled occupations and had adopted a westernized life style. In a later study at the Johannesburg General Hospital in 1970 Sefitel and Kew<sup>2</sup> found a prevalence rate of 0.6 per cent among 3 000 admissions to the medical wards. These authors concluded that the prevalence had increased as a result of westernized life style in an urban environment. A large proportion of their patients were cooks leading a sedentary life and they were frequently diabetic, hypertensive and had elevated serum lipids. In both these studies autopsy confirmation was available in 21 of the 54 cases.

Table II The racial prevalence of ischemic heart disease from various parts of South Africa

| Author            | Area      | Date | No of cases | IHD %  | Race   |
|-------------------|-----------|------|-------------|--------|--------|
| Schnre            | Cape Town | 1970 | 25 896      | 30     | Whites |
| Schnre            | Cape Town | 1970 | 4 485       | 14     | Black  |
| Schwartz et al    | Transvaal | 1958 | 20          | 0.4    | Black  |
| Sefitel et al     | Transvaal | 1963 | 417 000     | 0.01   | Black  |
| Sefitel and Kew   | Transvaal | 1970 | 3 600       | 0.6    | Black  |
| Cosnett           | Natal     | 1962 | 1 000       | 0.6    | Black  |
| Powell and Wright | Natal     | 1965 | 2 0         | 0      | Black  |
| Present series    | Natal     | 1975 | 10 553      | < 0.05 | Black† |

Autopsy confirmation in 1 of the 11 cases in both studies.  
†Coronary angiography in 3 of the 5 patients.

In Cape Town Schnre initially used rigid electrocardiographic criteria similar to those of Rose and Blackburn<sup>3</sup> in the diagnosis of myocardial infarction. Subsequently less stringent criteria were adopted and the diagnosis was made without the presence of pathological Q waves.<sup>4</sup> Among 4 485 patients a diagnosis of ischemic heart disease was considered present in 14 per cent, a figure much higher than reported from other centers. However autopsy confirmation or coronary arteriography was not available in this series.

Confirmation of the rarity of ischemic heart disease in the Black population is available from necropsy data. Thus, sudden death in Black patients is nearly always a result of cardiovascular syphilis.<sup>5</sup> Necropsy evidence of occlusive coronary atherosclerosis and myocardial infarction in subjects over the age of 30 has been found in only 1.5% of autopsies by Becker<sup>6</sup> \* 2.2% by Higginson et al<sup>7</sup> and 2.2% by Kalichurum.

To our knowledge there has been no report on the coronary arteriographic findings in Black patients in whom the diagnosis of myocardial infarction has been made electrocardiographically. In three of the 13 Black patients investigated by us the coronary arteries were found to be angiographically normal. We believe therefore that our prevalence rate is in fact less than 0.05 per cent and that the figures provided by other workers based on electrocardiographic evidence in the absence of autopsy confirmation or coronary arteriography are similarly too high.



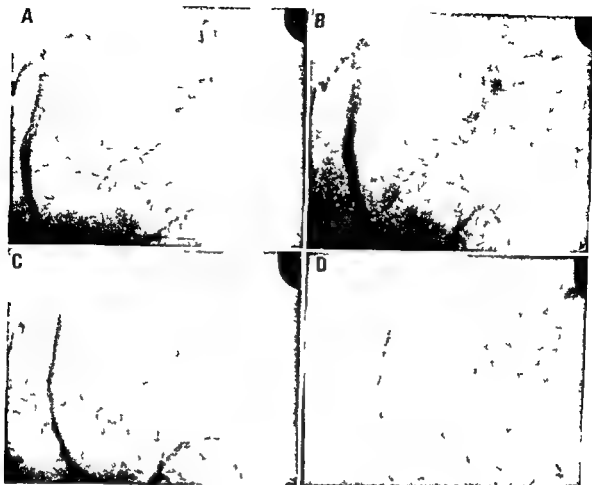


Fig 1 Selective right coronary arteriogram left anterior oblique view from a patient not included in this series. At the start of the injection (A) the right coronary artery is somewhat irregular but there is no significant stenotic lesion. Following withdrawal of the catheter there is progressive diffuse spasm of the entire right coronary artery almost to the point of obliteration (B, C and D).

Our findings suggest that a disproportionate number of our Black patients with myocardial infarction have angiographically normal coronary arteries. It is interesting that in our total experience with coronary arteriography since 1968 there have been only three examples of angiographically normal vessels in 787 angiograms performed on White patients. However, our White patients are almost invariably referred for this investigation because of angina pectoris refractory to beta blocker therapy, whereas the Black patients were referred electively for academic reasons because of the rarity of ischemic heart disease. It is possible that more frequent investigation of White patients who have made an uncomplicated recovery from myocardial infarction would reveal more cases with angiographically normal vessels. Our three White patients in fact fell into this category and were investigated because they were young and both they and members of their families had non

ejection clicks. They were shown to be examples of the billowing mitral leaflet syndrome.

Previously we have commented upon acute myocardial infarction with normal coronary arteries as a possible manifestation of the billowing mitral leaflet syndrome.<sup>1</sup> The electrocardiograms of these patients were characterized initially by pronounced elevation of the ST segments as occurs in Prinzmetal's angina. Coronary artery spasm provoked by the billowing mitral leaflet was considered as a possible cause. Alternatively, fibrin emboli emanating from the redundant mitral leaflets could be responsible and this could also account for major ischemic neurologic disturbances also associated with mitral leaflet prolapse.<sup>14</sup> In two of our Black patients in this series with normal coronary arteries there was also angiographic evidence of a billowing posterior leaflet and in one of these two a non-ejection click had been detected.

There is now considerable direct and indirect

evidence that coronary artery spasm may be responsible for myocardial ischemia. Several reports document the presence of normal coronary arteries in patients with variant angina and with documented myocardial infarction and angiographically demonstrable segmental left ventricular dysfunction. Coronary artery spasm has been noted with both angiographically diseased and with normal vessels.<sup>1,2</sup> Whereas proximal coronary artery spasm has occasionally been seen during coronary arteriography and is thought to be a result of mechanical stimulation by the catheter, diffuse spasm may be induced by the administration of ergonovine maleate and has been observed during withdrawal from nitroglycerine exposure.<sup>3</sup> We have observed spontaneous progressive diffuse spasm of a coronary artery following withdrawal of the injecting catheter from the vessel (Fig. 1).

In our 10 patients with occlusive atherosclerosis the angiographic pattern of lesions was similar to that seen in Whites. Three patients had single, five had double and three had triple vessel disease. The series is small but the clinical profile appears to be at variance with the characteristics observed by the Johannesburg workers. Thus the majority were manual laborers who were not diabetic, hypertensive or obese and could not be classified as westernized in their life style. The majority were however also young males. Their mean serum cholesterol level was 222 mg per cent, a figure similar to those with angiographically normal coronary arteries and a significant proportion of the urban Black population. Thus Walker<sup>4</sup> found that in the age group 30 to 39 years a serum cholesterol level above 220 mg per cent was present in 50 per cent of Whites, 25 per cent of urban and 10 per cent of rural Blacks.

Hypertension is common in the urban Black and is frequently accompanied by cerebrovascular and renal complications. Yet in a study of 500 patients over a period of 13 years Seedat and Reddy<sup>5</sup> found no examples of myocardial infarction complicating the disease. Even in the presence of severe aortic atherosclerosis in Black subjects involvement of the coronary and peripheral vessels is rarely seen. The immunity of the Black population to ischemic heart disease therefore remains an enigma. Our estimated prevalence rate of less than 0.1 per cent of medical admissions suggests that the disease is in fact no

more frequent than it was 15 years ago despite the effect of urbanization. Possibly a new look at mechanisms which protect the arterial wall and prevent the development of atherosclerosis in the face of other known accelerating factors may be rewarding.

### Summary

Thirteen Black patients who had classic electrocardiographic evidence of myocardial infarction supported by changes in serum enzymes were investigated by coronary arteriography. Ten of these had occlusive atherosclerosis and in none of these did the associated risk factors such as hypertension or diabetes appear to be operative and most were manual laborers. Their mean serum cholesterol measurement was found to be 222 mg per cent, a value which was found in 25 per cent of the urban Black population. In the remaining three patients the coronary arteries were found to be angiographically normal and two of these were associated with the billowing mitral leaflet syndrome. It is postulated that their myocardial infarction was a result of coronary spasm or a consequence of fibrin emboli emanating from the redundant mitral leaflets. Based on statistics from our major referring hospital it is estimated that the prevalence rate from myocardial infarction among general admissions to a medical ward is less than 0.1 per cent, a figure lower than previously reported by clinical electrocardiographic studies. It would appear that the prevalence of this disease has not increased over the last two decades and the immunity of the Black population is unexplained.

### REFERENCES

1. Schrire V. Heart disease in Southern Africa with special reference to ischemic heart disease. *S Afr Med J* 45:634, 1971.
2. Schwartz M B, Schamroth L, and Sefitel H C. The pattern of heart disease in the urbanised (Johannesburg) African. *Med Proc* 4:273, 1958.
3. Sefitel H C, Keeley K J, and Walker A R P. Characteristics of the South African Bantu who have suffered from myocardial infarction. *Am J Cardiol* 12:148, 1963.
4. Sefitel H C and Kew M C. Myocardial infarction in the Johannesburg Bantu. *S Afr Med J* 44:8, 1970.
5. Cornett J E. Heart disease in the Zulu, especially cardiomyopathy and cardiac infarction. *Br Heart J* 24:16, 1967.
6. Powell S J and Wright R. Cardiomyopathy in Durban. *S Afr Med J* 39:1062, 1965.
7. Rose G A and Blackburn H. Cardiovascular survey

- methods Monograph Series No 56 Geneva 1968 WHO
- 8 Becker E J P Cardiovascular disease in the Bantu and Coloured races of South Africa *S Afr J Med Sci* 11 97 1946
- 9 Becker E J P Cardiovascular disease in the Bantu and Coloured races of South Africa Incidence pathology and general features *S Afr J Med Sci* 11 1 1946
- 10 Higgs-Jones J Isaacson C and Simpson I Pathology of cryptogenic heart disease *Arch Pathol* 70 497 1960
- 11 Kallichurum S Death caused by heart failure in the Bantu in Durban *S Afr Med J* 43 214 1969
- 12 Chesler E Matisonn R E Lakier J B Pocock W A Obel I W P and Barlow J B Acute myocardial infarction with normal coronary arteries A possible manifestation of the billowing mitral leaflet syndrome *Circulation* 54 203 1976
- 13 Malcolm A D Boughner D R Kostuk W J and Ahuja S P Clinical features and investigative findings in presence of mitral leaflet prolapse Study of 85 consecutive patients *Br Heart J* 38 244 1976
- 14 Potts H Steyn P D and Houk C Transmural myocardial infarction with arteriographically normal appearing coronary arteries *Chest* 62 549 1972
- 15 Khan A H and Haywood L J Myocardial infarction in 11 patients with radiologically patent coronary arteries *N Engl J Med* 291 427 1974
- 16 Higgins C H Weider L Silverman J S and Schroeder J S Clinical and arteriographic features of Prinzmetal's variant angina Documentation of etiologic factors *Am J Cardiol* 37 831 1976
- 17 Wiener L Kasprarian H Duca P R Walinsky P Gottlieb R S Hanckel S and Brest A N Spectrum of coronary arterial spasm Clinical angiographic and myocardial metabolic experience in 29 cases *Am J Cardiol* 38 945 1976
- 18 Lange R L Reid M S Treach D D Keelan M H Bernhard V N and Coolidge G Non atheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerine exposure *Circulation* 46 666 1972
- 19 Walker A R P Studies bearing on coronary heart disease in South African populations *S Afr Med J* 47 85 1973
- 20 Seedat Y K and Reddy J A Study of 1000 South African Non White hypertensive patients *S Afr Med J* 48 816 1974
- 21 Reef H and Isaacson C Atherosclerosis in the Bantu The distribution of atheromatous lesions in Africans over 50 years of age *Circulation* 25 66 1962
- 22 Corday E and Corday S R Prevention of heart disease II *Am J Cardiol* 37 461 1976

# Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center Inc, P O Box 767, Schenectady, NY 12301 518 374 4430. For copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law, this consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works, or for resale.

# Four year follow up of Black schoolchildren with non ejection systolic clicks and mitral systolic murmurs

Morris Cohen MB  
Wendy A Pocock MB  
Jeffrey B Lakier MD  
Margaret J McLaren MB  
Anthony S Lachman MB  
John B Barlow MD  
*Johannesburg South Africa*

In 1972 a survey was undertaken by this unit on Black schoolchildren in the South Western Townships (Soweto) near Johannesburg with the primary objective of determining the prevalence of rheumatic heart disease in that population. A total of 12 050 children randomly selected to represent a school population of about 99 000 were auscultated by 10 trained or trainee cardiologists. Rheumatic heart disease was detected in 168 children yielding an optimally weighted prevalence rate of 6.9 per thousand. One hundred and sixty eight children yielding an overall prevalence rate in the sample school population of 14 per thousand had a non ejection systolic click (NESC) a late systolic murmur or both. We had thought this a high prevalence of these auscultatory features and had wondered whether many were not suffering from early rheumatic heart disease. A follow up study of these 168 children was clearly indicated.

The present study was therefore undertaken with the primary objective to determine by clinical examination and careful auscultation the current status of the 168 children or as many as could be traced after a four year period during which they had received no prophylaxis against

rheumatic activity. The investigation also provided an opportunity to examine equally carefully the same number of age and sex matched control Black schoolchildren in order to reassess the prevalence of NESCs and mitral systolic murmurs in this population group.

## Methods

The subjects were visited personally by one of us (M.C.) at their homes in Soweto and where possible the proposed investigation was discussed with both the children and their parents. Appointments were made for examination at Baragwanath Hospital during February 1976. Of the 168 children who had had an NESC or late systolic murmur in 1972 the record files of three had been mislaid. Six children could not be traced, four were seen in their homes and appeared well but refused examination and 16 were reputed to be well but were at boarding school outside the Johannesburg area. Examination of the 16 boarding school children had been planned for July 1976 but due to civil unrest and rioting in Soweto this was not possible. Nevertheless eight of the 16 children did attend Baragwanath Hospital during July 1976 and were examined for us by two cardiologists.

One hundred and thirty nine subjects (91 females, 48 males) were thus available for examination during February 1976 together with the same number of age and sex matched controls. The ages ranged from six to 21 years with a mean age of 15 years. The cardiovascular system was examined by J.B.B. who at all times was unaware as to whether the child was a 1972

From the Cardiology Clinic, Johannesburg and Baragwanath Hospital (the Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa).

Supported by grant from the Sir Isaac Isaacs Foundation Trust, Cardiology, University of the Witwatersrand.

Received for publication May 18, 1977.

Accepted for publication May 26, 1977.

Reprint requests: Professor J.B. Barlow, Cardiology Clinic, Johannesburg, 11 April 1978, Johannesburg, South Africa.

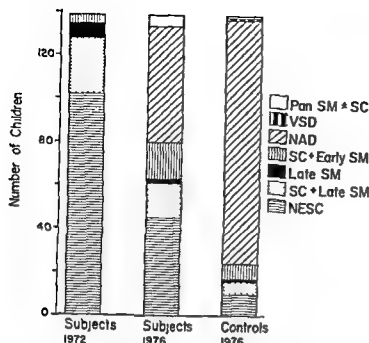


Fig 1 Histogram showing the auscultatory features of the 139 subjects in 1972 and on re auscultation in 1976 together with the auscultatory features of the 139 control children. For full description see text. Pan SM + SC = pansystolic murmur  $\pm$  non ejection systolic click VSD = ventricular septal defect NAD = no abnormality detected SC + Early SM = non ejection systolic click and early systolic murmur Late SM = late systolic murmur SC + Late SM = non ejection systolic click and late systolic murmur NESC = non ejection systolic click

subject or a 1976 control. Any abnormality of the thoracic cage was noted. A 12 lead electrocardiogram was recorded by a technologist, but was not seen by the examiner. The electrocardiograms were later reported by J. B. L. who, in turn, was unaware of the auscultatory findings and to which group the child belonged.

All children were auscultated in the supine, left lateral erect and squatting positions. The examination was never completed in less than three minutes; usually took five to eight minutes and occasionally lasted 15 minutes or longer. Auscultation was thus performed in more detail than is customary for a routine check or for the elucidation of a systolic murmur and certainly more carefully than during our 1972 study. The findings were documented to describe all sounds, murmurs and clicks, their nature and intensity as well as the site at which they were heard and any alterations with changes in posture. The NESC's were classified into three groups: (1) Those that were easily heard and were usually loud (2+); (2) Those that were also definitely present but were soft and not as easily heard (1+); (3) Those that

were possibly present having been heard for a few beats and not infrequently after a change in posture, but which could not be confirmed on further or repeated auscultation. Children in this latter group, of whom there were as many as 16.6 per cent in the controls and 13.7 per cent in the subjects, are included in our analysis as normal on auscultation.

## Results

**Subject group** The auscultatory features of the 139 subject children in 1972 are shown in Fig 1 which also illustrates the status on re-examination in 1976. One hundred and two children had had an isolated NESC, 26 a NESC with an associated late systolic murmur, seven an isolated late systolic murmur and four a NESC with an early nonpansystolic murmur, thought to denote mitral regurgitation. In 1976, 45 children had an isolated NESC, 16 a NESC and late systolic murmur, two an isolated late systolic murmur, 16 a NESC and early systolic murmur, five had a pansystolic murmur of whom three had an associated NESC and as many as 55 (39.5 per cent) were passed as normal. In 33 subjects the NESC was 1+ and in 47 it was classified as 2+. In only nine of the 80 subjects with a NESC was the click first heard or only heard in a position other than recumbent. Only one of the five children with a pansystolic murmur had moderate mitral regurgitation and that child also had a markedly depressed sternum. The remaining four children with pansystolic murmurs were assessed as having mild mitral regurgitation. In one of the latter the murmur was pansystolic in the standing position only.

Fig 2 shows the changes in the auscultatory features of the main subdivisions of 1972 as found on re-auscultation in 1976. The 55 children now found to be normal came from each of the four subdivisions: namely 44 of 102 with isolated NESC's (43 per cent), eight of 26 with NESC's and late systolic murmurs (30.7 per cent), two of seven with isolated late systolic murmurs (28.5 per cent) and one of four with a NESC and early systolic murmur (25 per cent). Furthermore there was no specific trend as each subdivision on re-auscultation showed a whole spectrum of auscultatory features.

Of the 16 children at boarding school, eight (six female) were examined by two cardiologists at

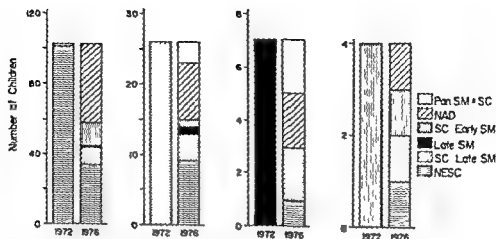


Fig 2 Histogram showing the breakdown in each category of the auscultatory features of the subject group in 1976 as compared to those present in 1972. For full description see text

Baragwanath Hospital during July 1976. No deterioration was found in any while one was assessed as normal.

**Control group** The auscultatory features detected in the 139 age and sex matched controls are also shown in Fig 1. One hundred and thirteen were normal and one had the typical auscultatory features of a small ventricular septal defect. One child had an isolated late systolic murmur and another had a pansystolic murmur of mitral regurgitation in the standing position without an associated NESC. Twenty-three children had NESC, 13 of whom had associated mitral systolic murmurs. The NESC was assessed as 2+ in six children and 1+ in the remaining 17. In only two of the 23 was the NESC present or first heard in a position other than recumbent.

**Thoracic cage deformities** Twenty-eight of the 139 subjects were found to have a narrow antero-posterior chest diameter and 16 of these had a NESC (57.1 per cent). Seventeen in the control group had a narrow chest diameter, seven of whom had a NESC (41.2 per cent). The prevalence of NESC in the subject and control groups without a chest deformity was 57.6 per cent and 13.3 per cent respectively.

**Electrocardiograms** ST and T wave abnormalities were detected in two subjects and two controls. The typical pattern of inferior ischemia was present in the two subjects, both of whom had a NESC. One control assessed as normal on auscultation had deep T wave inversion from V<sub>1</sub> to V<sub>6</sub>, whereas the other who had a

NESC and early systolic murmur showed the pattern of inferior ischemia together with T wave inversion from V<sub>1</sub> to V<sub>6</sub>. A child in the subject group with a NESC and a late systolic murmur had a wandering atrial pacemaker with nodal escape beats. Another subject passed as normal on auscultation in 1976 had occasional supraventricular ectopic beats and one premature ventricular contraction.

### Discussion

The results of this blind controlled study have yielded meaningful and to us somewhat surprising information on the prevalence of NESC and mitral systolic murmurs in Black schoolchildren. Of the 139 controls examined, 23 (16.5 per cent) had a NESC and if the two with isolated mitral systolic murmurs are included, 25 (17.9 per cent) had auscultatory features compatible with mitral valve prolapse. A very high prevalence in normals has however been reported in other recent studies. Markiewicz and colleagues, in an investigation of 100 healthy female volunteers, found a 17 per cent prevalence of NESC and/or late or mid to late systolic murmurs on phonocardiograms recorded supine in the upright position or after inhalation of amyl nitrite. Ten women had both auscultatory and echocardiographic evidence of mitral valve prolapse while 18 others had either echocardiographic or phonocardiographic findings suggestive of the mitral valve abnormality. Procacci and co-workers reported a prevalence of 63 per cent (74 of 1163 adult

females) on auscultation and mitral valve prolapse was confirmed using echocardiography in 60 of the 74 women Brown and associates<sup>5</sup> found echocardiographic evidence of prolapse in 6 per cent of 520 women with no history of heart disease. These surveys suggested a much higher prevalence of mitral valve prolapse than had been reported previously either from our own laboratory<sup>1</sup> or by others. The more than tenfold increase in prevalence detected among the 139 controls in our present study as compared to the larger survey in 1972<sup>1</sup> requires explanation. It may partly be accounted for by the fact that only 10 per cent of the 12 050 children had been postured auscultation was necessarily hurried, the primary objective was the detection of rheumatic heart disease and some of the auscultators were relatively inexperienced. In the present investigation on the other hand auscultation was detailed, prolonged, and undertaken in quiet and comfortable surroundings by an experienced auscultator who was listening specifically for these auscultatory features. Had echocardiography been performed it is possible that more instances of mitral valve prolapse would have been detected since the entity of silent prolapse is accepted by some workers.<sup>10</sup>

The significance of such a high prevalence rate of these auscultatory features in apparently normal children and young adults is uncertain at the present time and in some instances may represent a normal variant.<sup>1</sup> In view of this and the rarity of infective endocarditis in subjects who have not taken prophylaxis,<sup>1</sup> there is some doubt as to whether prophylaxis is indicated in all cases. Infective endocarditis has indeed supervened in patients with an isolated NESC<sup>11-13</sup> but it is now apparent that this complication is rare in relation to the high prevalence of the physical sign. Although we previously advised prophylaxis<sup>13-14</sup> in all patients with an isolated NESC this is often impracticable and may be unnecessary. Perhaps prophylaxis against infective endocarditis should be recommended only in instances where there is a constant mitral systolic murmur.

The etiology of the mitral valve abnormality in the subject group is not known. Although we had suggested that mild rheumatic heart disease was the probable underlying cause in a large proportion of the 168 children with NESCs and late systolic murmurs detected in that survey their

subsequent course has not supported our postulate. During the four years since the survey was completed none of the subjects was on prophylaxis against rheumatic fever yet 55 were normal on re-examination and only one showed significant deterioration. That patient has a markedly depressed sternum and may represent a forme fruste of the Marfan syndrome. Four others may have deteriorated slightly in that they now have soft pansystolic murmurs. In all of the four the mitral regurgitation was assessed as mild. It is probable that the majority of both subjects and controls with the auscultatory features of a NESC and/or early late or pansystolic murmurs of mitral regurgitation have 'idiopathic' prolapse, albeit mild, and that a few will in time manifest features of the specific billowing mitral leaflet syndrome.<sup>11-14</sup> Electrocardiographic abnormalities compatible with the syndrome were present in a small number in both groups and thoracic cage abnormalities which are a recognized accompaniment of mitral valve prolapse,<sup>11-14</sup> were slightly more common in the subject group.

The results of this four year follow up of the subject group is in keeping with the generally benign prognosis<sup>11-14</sup> of the billowing mitral leaflet syndrome. Reassessment at a later date of both groups would clarify the natural history of these auscultatory features in young urban Blacks.

### Summary

In 1972 we conducted a survey of 12 050 urban Black schoolchildren and detected 168 (prevalence rate of 14 per 1 000) with a non-ejection systolic click (NESC) a late systolic murmur or both. The etiology of the mitral valve abnormality was unknown but we considered that a significant proportion might have early rheumatic heart disease.

The auscultatory features four years later of 139 of the original 168 subjects as well as those of 139 age and sex matched controls are presented in this study. No cardiac abnormality was detected in as many as 55 of the subjects. Five children now had pansystolic murmurs but the mitral regurgitation was assessed as mild in four. Twenty-five (17.9 per cent) of the controls, 23 of whom had NESCs had auscultatory features compatible with mitral valve prolapse.

These findings do not support our earlier

suggestion that a large number of the 1972 subjects have mild rheumatic heart disease. The results are in accord with other studies which have indicated that auscultatory features compatible with mitral valve prolapse are common in normals and also that the prognosis of the specific billowing mitral leaflet syndrome is generally benign.

We thank Dr P J Beukes Medical Superintendent Baragwanath Hospital for his co-operation. We are indebted to Dr A Bakst and Dr D M Bramwell-Jones for examining the boarding school children and to Miss P A Palfrey, Miss K C Haverley, Miss W Khonzaphu and Mrs I N Thebehali for technical and secretarial assistance.

## REFERENCES

- 1 McLaren M J, Hawkins D M, Koornhof H J, Bloom K H, Bramwell-Jones D M, Cohen E, Gale G E, Fanarek K, Lachman A S, Lakier J B, Pocock W A and Barlow J B. Epidemiology of rheumatic heart disease in black schoolchildren of Soweto, Johannesburg. *Br Med J* 3 4:4 1975.
- 2 McLaren M J, Hawkins D M, Lachman A S, Lakier J B, Pocock W A and Barlow J B. Non-ejection systolic clicks and mitral systolic murmurs in black schoolchildren of Soweto, Johannesburg. *Br Heart J* 38 718 1976.
- 3 Markiewicz W, Stoner J, London E, Hunt S A and Popp H L. Mitral valve prolapse in one hundred presumably healthy young females. *Circulation* 53 464 1976.
- 4 Proccacci P M, Savran S V, Schreier S L and Bryson A L. Prevalence of clinical mitral valve prolapse in 1160 young women. *N Engl J Med* 294 1086 1976.
- 5 Brown O H, Kloster F E and De Moia H. Incidence of mitral valve prolapse in the asymptomatic normal (Abstr). *Circulation* 51 and 52 (Suppl 1): 1177 1975.
- 6 Rizzon P, Biasco G, Brindici G and Mauro F. Familial syndrome of mid systolic click and late systolic murmur. *Br Heart J* 25 745 1973.
- 7 Jernatv H M. Mitral valve prolapse-click syndrome. *Progr Cardiovasc Dis* 15 673 1973.
- 8 Popp R L, Brown O H, Silverman J F and Harrison D C. Echocardiographic abnormalities in the mitral valve prolapse syndrome. *Circulation* 49 478 1974.
- 9 Hurst J W. Mitral valve prolapse-click syndrome—II (Letter). *Am J Cardiol* 38 21 1976.
- 10 Malcolm A D, Boughner D R, Koetuk W J and Ahuja S P. Clinical features and investigative findings in presence of mitral leaflet prolapse. Study of 85 consecutive patients. *Br Heart J* 38 244 1976.
- 11 Le Bauer E J, Perloff J K and Keliber T F. The isolated systolic click with bacterial endocarditis. *Am Heart J* 73 534 1967.
- 12 Harvey W P. Comment in Year Book of Cardiovascular Medicine and Surgery, edited by Braunwald E., Harvey W P, Kirkendall W M, Kirklin J W., Nadas A S, Paul M and Wright I S. Chicago 1977. Year Book Medical Publishers Inc. p 131.
- 13 Lachman A S, Bramwell-Jones D M, Lakier J B, Pocock W A and Barlow J B. Infective endocarditis in the billowing mitral leaflet syndrome. *Br Heart J* 37 326 1975.
- 14 Barlow J B and Pocock W A. The problem of nonejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am Heart J* 90 636 1975.
- 15 Cobbs H W Jr. Clinical recognition and medical management of rheumatic heart disease and other acquired valvular disease. In *The Heart*, ed J edited by Hurst J W, Logue R B, Schlant R C and Wegener N K. New York 1974. McGraw Hill Book Company, Inc. p 683.
- 16 Chesler E, Mattson R E, Lakier J B, Pocock W A, Obel I W P and Barlow J B. Acute myocardial infarction with normal coronary arteries: A possible manifestation of the billowing mitral leaflet syndrome. *Circulation* 54 203 1976.
- 17 Bon Tempo, C P, Ronan J A, de Leon A C and Twiggs H L. Radiographic appearance of the thorax in systolic click late systolic murmur syndrome. *Am J Cardiol* 36 2 1975.
- 18 Salmon J, Shah P M and Heine R A. Thoracic skeletal abnormalities in idiopathic mitral valve prolapse. *Am J Cardiol* 36 37 1975.
- 19 Allen H, Harris A and Leatham A. Significance and prognosis of an isolated late systolic murmur: a 9 to 27 year follow up. *Br Heart J* 36 525 1974.
- 20 Leach M. Mitral valve prolapse: a clinical spectrum (Editorial). *N Engl J Med* 294 111 1976.



# Significance of a terminal R wave in Lead V<sub>1</sub> of the electrocardiogram

H Raunio MD  
V Rissanen, MD  
C Jokinen MD  
O Penttilä MD

Kuopio, Finland

A high amplitude terminal R wave associated with a broadened QRS complex in Lead V<sub>1</sub> is generally accepted as an ECG sign of a complete block in the right bundle branch, while a terminal r wave of low amplitude has turned out to be an ambiguous ECG pattern. In most electrocardiographic textbooks a terminal r wave of low amplitude in Lead V<sub>1</sub>, together with a prominent S wave in Leads V<sub>1</sub> and V<sub>2</sub>, and the QRS duration from 0.09 sec to 0.11 sec are defined to indicate an incomplete right bundle branch block (ICRBBB).<sup>1-14, 29</sup>

Several mechanisms have been suggested to cause a terminal r wave of low amplitude in Lead V<sub>1</sub>. Experimentally a partial conduction delay in the right bundle branch has been shown to cause an rSr' pattern.<sup>10</sup> On the other hand, according to Moore and associates<sup>12</sup> this pattern can occur in right ventricular hypertrophy where conduction in the right bundle branch is normal. Furthermore, in clinicopathological correlative studies Lenégre found that the right bundle branch was histologically normal in 76 per cent of the 33 patients with an ICRBBB pattern and that 94 per cent of them had a hypertrophied right ventricle.<sup>11</sup> Also several other authors have suggested that the terminal r wave in Lead V<sub>1</sub> may be associated with right ventricular hypertrophy.<sup>2, 5, 10, 13, 17, 18, 27, \*</sup> It may also develop in connexion with a myocardial infarction or left ventricular hypertrophy.<sup>1, 6, 7, 14, 15, \*</sup> The clinical

significance of the terminal r wave in Lead V<sub>1</sub> and its relationship to various cardiopulmonary combinations has not been fully evaluated. In the present study we have analyzed the occurrence of the terminal r wave in Lead V<sub>1</sub> in healthy children and young adults as well as in middle aged and elderly patients with or without autopsy evidence of a cardiopulmonary disease.

## Material and methods

The series is composed of the following groups:

Group I: 104 healthy children aged 3 to 14 years. The mean age 8.5 years.

Group II: 207 healthy students: 107 men and 100 women aged 20 to 30 years. The mean age 24.3 years.

Group III: 171 hospital patients: 62 men and 109 women aged 30 to 85 years who died with no autopsy evidence of a pulmonary or cardiac disease. The mean age 55.5 years.

Group IV: 1,078 hospital patients: 677 men and 401 women aged 30 to 92 years with a pulmonary and/or cardiac disease verified at autopsy. The mean age 63.4 years.

Characteristics of Groups III and IV have been described in a previous paper.<sup>1</sup>

**Electrocardiogram** The ECGs were recorded with standard direct writing instruments. One was a heated stylus recording instrument with a frequency response of 0 to 150 Hz (Cardiopan 3\*) and the other an ink-jet recorder with a frequency response of 0 to 700 Hz (Orli 326f). Cases with a complete right or left bundle branch

From the Department of Medicine, University of Kuopio, Kuopio, Finland.

Received for publication March 15, 1977.

Accepted for publication Apr. 11, 1977.

Reprint requests: Dr H. Raunio, Department of Medicine, University of Kuopio, SF-70210 Kuopio 21, Finland.

F. Lechti AG, Bern, Switzerland  
Tollu Medical Electronics, Helsinki, Finland

block as well as those with a WPW syndrome or idioventricular rhythm were excluded from the study

A terminal r wave in Lead V<sub>1</sub> was defined as follows: the positive height more than 1 mm but less than 6 mm when the succeeding ST segment was used as a reference line. The terminal r wave had to appear in every QRS complex of Lead V<sub>1</sub>. The cases were divided into three types (Fig 1).

Type A The terminal r wave lower than the initial one in the same complex

Type B The terminal r wave higher than the initial one

Type C Cases with a Qr pattern in Lead V

An initial r wave was considered not to be present if it was lower than 0.25 mm. Cases with the R/S equal to or greater than 1 in Lead V as well as those with an r' wave followed by a terminal r wave (rsr's) were excluded. The ECG criteria of right ventricular hypertrophy (RVH) defined by Roman and colleagues<sup>4</sup> were used.

**Autopsy data** Autopsy data on the hospital patients were based on routine autopsy protocols. In postmortem examination enlargement of the heart, right and left ventricular hypertrophy and signs of valvular or congenital heart disease were noted. Five mm and 15 mm were determined as maximum thicknesses for the normal right and left ventricular walls. Macroscopical evidence of significant pulmonary disease and the size and location of the myocardial infarction were recorded. When necessary, samples from the pulmonary or myocardial lesions were taken for microscopy.

## Results

**A terminal r wave in Lead V in relation to age** The occurrence of a terminal r wave of type A in Lead V decreased with age in healthy children, healthy young adults and middle aged and elderly subjects without autopsy evidence of a cardiopulmonary disease (Table I). The QRS duration in children was from 0.06 sec to 0.07 sec and in healthy adults from 0.09 sec to 0.11 sec.

**A terminal r wave in Lead V in relation to a cardiopulmonary disease** A terminal r wave in Lead V was found in 59 per cent (53 per cent in men and 70 per cent in women) of the middle aged and elderly patients in whom the autopsy revealed a significant pulmonary and/or cardiac disease (Table I).



Fig 1 Schematic presentation of type A, B, and C deformities of the QRS complex in Lead V<sub>1</sub>

QRS deformities of types B and C were found only in patients with a cardiopulmonary disease while type A occurred in patients with or without autopsy evidence of cardiopulmonary disease. In middle aged and elderly patients the prevalence of the A type deformity was the same (0.6 per cent) whether a cardiopulmonary disease was present or not. No sex difference was found.

The terminal r wave in Lead V<sub>1</sub> was found in 83 per cent of patients with right ventricular overload, in 29 per cent of patients with left ventricular disease but no right ventricular overload and in 51 per cent of patients with both ventricles diseased (Table II). In 42 per cent of cases with a terminal r wave in Lead V<sub>1</sub>, the free wall of the right ventricle was hypertrophied (Table II). This was the case in 30 per cent of cases with the B type and in 57 per cent of those with the C type deformity. In not one case of the A type deformity was the right ventricle hypertrophied. On the other hand, the autopsy revealed a hypertrophied right ventricle in only 15 per cent of the middle aged and elderly patients with a cardiopulmonary disease in whose ECG no terminal r wave in Lead V<sub>1</sub> could be observed. The highest frequency (10 per cent) of the terminal r wave in Lead V<sub>1</sub> was found in pulmonary patients with no myocardial infarction (Table II). The QRS duration in pulmonary patients with a terminal r wave was from 0.07 sec to 0.11 sec. In half of them the autopsy revealed a hypertrophied right ventricle (Table II). In five cases of type B and in nine cases of type C the terminal r wave was the only ECG sign indicating right ventricular hypertrophy.

There were seven cases with a terminal r wave where a myocardial infarction but no right ventricular disease was found. In two cases the infarct was on the anterior and in one case on the posterior wall of the left ventricle. Four patients had a combined anteroposterior myocardial infarction. In four of the seven patients the

Table 1 Occurrence of a terminal r wave in Lead V<sub>1</sub>

| Series studied  | Total number of cases |     | Number of cases with a terminal r wave in Lead V <sub>1</sub> |   |  |    |                |    |                 |          |
|---|-----------------------|-----|---|---|--|----|----------------|----|-----------------|----------|
|   |                       |     | Type A terminal r wave lower than the initial one             |   | Type B terminal r wave higher than the initial one |    | Type C Qr type |    | Total           |          |
|   | M                     | F   | M   | F | M  | F  | M              | F  | Number of cases | Per cent |
| Group I Healthy children  | 61                    | 43  | 1   | 2 | —  | —  | —              | —  | 3               | 2.9      |
| Group II Healthy young adults                                       | 107                   | 100 | 1   | 2 | —  | —  | —              | —  | 3               | 1.4      |
| Group III Autopsy cases with no evidence of cardiopulmonary disease | 62                    | 109 | 1   | — | —  | —  | —              | —  | 1               | 0.6      |
| Group IV Cases with autopsy evidence of cardiopulmonary disease     | 677                   | 401 | 4   | 2 | 12   | 11 | 20             | 15 | 64              | 5.9      |

duration of the QRS was 0.12 sec or 0.13 sec but the shape of the QRS complex did not indicate a complete right nor complete left bundle branch block. All of these four cases had an infarction on the anterior wall of the left ventricle. The material also included six patients with the terminal r wave in Lead V<sub>1</sub> associated with left ventricular hypertrophy but no myocardial infarction (three cases of aortic valvular stenosis, three cases of cardiomyopathy). The free wall of the right ventricle was within normal limits in these cases, and the QRS duration was from 0.09 sec to 0.11 sec.

### Discussion

Two types of deformities: rsr and rsr's in the QRS complex in Lead V<sub>1</sub> can occur. They both have generally been linked with ICRBBB. In the first type the terminal QRS forces are directed forwards and in the latter backwards. According to Guller and associates<sup>1</sup> the backward directed terminal QRS forces are found in healthy children while the former type is associated with right ventricular hypertrophy. The rsr's type also seemed to show greater positional and respiratory changes<sup>1</sup> and has frequently (49 per cent) been found in healthy athletes who failed to show the rsr pattern.<sup>1</sup> As these two types thus have different characteristics we limited the study only to the rsr deformity in Lead V<sub>1</sub>.

A terminal r wave in Lead V<sub>1</sub> has been found in up to 5 per cent of the ECGs of healthy children<sup>1, 20</sup> while it was an uncommon (0.2 per cent)

finding in healthy adults.<sup>1</sup> In the present study the occurrence seemed to decline with age: 2.9 per cent in children, 1.4 per cent in young adults, 0.6 per cent in middle aged and elderly subjects with no cardiopulmonary disease. There are only a few studies where the terminal r waves in Lead V<sub>1</sub> are divided in different groups on the basis of comparison with the height of the initial r wave of the same complex.<sup>21-24</sup> In a Finnish population study on subjects aged 30 to 59 years the A type pattern as defined in this study was found in 2.9 per cent of men and 1.5 per cent of women and the B type pattern was found in 0.8 per cent of men and 0.6 per cent of women.

The findings of the present study show that the A type deformity appears in the same frequency in healthy subjects as in subjects suffering from a cardiopulmonary disease and that type A is not associated with RVH. On the other hand B and C type deformities did not occur in this study in subjects without evidence of a cardiopulmonary disease. Our findings show further that the occurrence of the terminal r wave of type B or C in Lead V<sub>1</sub> is frequently involved with right ventricular hypertrophy. Thus we can rightly presume that the terminal r wave higher than the initial one in middle aged and elderly subjects is an ECG sign pointing to a pathological state while an r wave lower than the initial one seems to be an innocent ECG finding. Although we have not made histological studies of the right bundle branch we agree with Massing and James<sup>21</sup> and with Moore and colleagues<sup>1</sup> and regard it as

Table II Occurrence of the different types of terminal positivity in Lead V<sub>1</sub> in 1078 subjects with autopsy evidence of significant pulmonary and/or left ventricular disease

| Autopsy findings  | Number of cases with a terminal r wave in Lead V <sub>1</sub> |       |   |       |  |       |                |       |                 |         |
|---|---|-------|---|-------|--|-------|----------------|-------|-----------------|---------|
|   | Total number of cases   |       | Type A terminal r wave lower than the initial one |       | Type B terminal r wave higher than the initial one |       | Type C Qr type |       | Total           |         |
|   |   |       | No  | (RVH) | No   | (RVH) | No             | (RVH) | Number of cases | (RVH) % |
| Pulmonary disease without a myocardial infarction or valvular heart disease         | 311   | (68)  | 2   | (—)   | 11   | (3)   | 17             | (13)  | 30              | (16)    |
| Pulmonary disease with a myocardial infarction                                      | 123   | (17)  | 1   | (—)   | 1  | (—)   | 1              | (1)   | 3               | (1)     |
| Pulmonary thromboembolism without a myocardial infarction or valvular heart disease | 165   | (96)  | —   | (—)   | 4  | (2)   | 7              | (3)   | 11              | (5)     |
| Pulmonary thromboembolism with a myocardial infarction                              | 69  | (13)  | 1   | (—)   | 1  | (—)   | 3              | (1)   | 5               | (1)     |
| Valvular heart disease†   | 93  | (21)  | —   | (—)   | 0  | (—)   | 3              | (1)   | 5               | (1)     |
| Congenital heart disease  | 5   | (2)   | —   | (—)   | —  | (—)   | —              | (—)   | —               | (—)     |
| A myocardial infarction but no pulmonary disease                                    | 18  | (93)  | 1   | (—)   | 0  | (0)   | 4              | (1)   | 7               | (3)     |
| Coronary arteriosclerosis but no myocardial infarction                              | 4*  | (—)   | —   | (—)   | —  | (—)   | —              | (—)   | —               | (—)     |
| Left ventricular hypertrophy and cardiomyopathy                                     | 9   | (10)  | 1   | (—)   | 2  | (—)   | —              | (—)   | 3               | (—)     |
| Total   | 108   | (180) | 6   | (—)   | 23   | (7)   | 30             | (20)  | 64              | (27)    |

Figures in the parentheses indicate the number of cases with RVH found at autopsy.  
 \*5 patients in this group had an additional pulmonary disease.

misleading and incorrect to consider all cases with a terminal r wave in Lead V indicative of only ICRBBB.

A terminal r wave in Lead V of type B or C sometimes occurs in pulmonary patients without evidence of a hypertrophied free wall of the right ventricle. In these cases the hypertrophied outflow tract of the right ventricle may be the origin of the r patterns. As expected right ventricular hypertrophy appears more frequently in patients with a C than with a B type deformity. Type C is a final state of right ventricular overload and develops when the initial r wave disappears secondary to the rotation of the heart.

A terminal r wave in Lead V was also found in some patients with left ventricular but no right ventricular disease. It appeared in cases of an anterior myocardial infarction involved with a pen infarction block<sup>20</sup> and in some cases of strictly posterior myocardial infarctions.<sup>21</sup> In the presence of a pen infarction block the QRS duration may be prolonged. On the other hand in

cases of left anterior hemiblock the terminal r waves tend to appear if the right precordial leads are recorded higher than usual.<sup>22</sup>

It is concluded that the height of the terminal r wave in Lead V in subjects over 30 years of age has clinical significance if it is higher than the initial r wave in the same complex. It is frequently associated with right ventricular overloading disease like right ventricular hypertrophy and sometimes with left ventricular disease. A terminal r wave in Lead V<sub>1</sub> lower than the initial one tends to be an innocent finding.

#### Summary

A terminal r wave in Lead V lower than 0.6 mV was studied in the ECGs of four groups: (1) 104 healthy children; (2) 207 healthy young adults; (3) 171 patients with no autopsy evidence of a cardiopulmonary disease; and (4) 1078 autopsy patients with a cardiopulmonary disease. Cases with a complete right bundle branch block were excluded. A terminal r wave occurred in 2.9

per cent of healthy children, 14 per cent of healthy young adults 0.6 per cent of patients without and in 5.9 per cent of patients with autopsy evidence of a cardiopulmonary disease

The occurrence of a terminal r wave was most common in pulmonary patients (10 per cent) But it was also found in patients with an anterior or a posterior myocardial infarction and in some cases of left ventricular hypertrophy

In the autopsy series RVH occurred in 57 per cent of patients with a Qr pattern, in 30 per cent of patients with a terminal r wave higher than the initial one, and in none of the patients with a terminal r wave lower than the initial one

It is concluded that the height of the terminal r wave has clinical significance A terminal r wave higher than the initial one in Lead V<sub>1</sub> is associated with a cardiopulmonary disease in subjects over 30 years of age while an r wave lower than the initial one seems to be an innocent finding

# REFERENCES

- Barker J M and Valencia F The precordial electrocardiogram in incomplete right bundle branch block *Am Heart J* 38 376 1949
- Braunwald E Donoso E Sapin S O and Grishman A Right bundle branch block Hemodynamic vector cardiographic and electrocardiographic observations *Circulation* 13 866 1956
- Burch G E and DePasquale N P The electrocardiographic diagnosis of pulmonary heart disease *Am J Cardiol* 11 622 1963
- Burch G E and DePasquale N P Electrocardiography in the diagnosis of congenital heart disease Philadelphia 1967 Lea & Febiger Publishers
- Coelho E Amram S S Sa A B Mendes J C F and Tavares V Electrocardiographic and vectorcardiographic alterations in chronic cor pulmonale *Am J Cardiol* 10 20 1962
- Flowers N C and Horan L G Mid and late changes in the QRS complex in Advances in electrocardiography Schlant R C and Hurst J W eds New York and London 1972 Grune & Stratton Inc
- Grant R P Clinical electrocardiography New York 1957 McGraw Hill Book Company Inc
- Guller B Berg K L M Weidman W H O'Brien P C Dushane J W and Smith R E Computer interpretation of Frank vectorcardiogram in normal newborns identification of right ventricular dominance patterns *J Electrocardiol* 5 307 1972
- Hus R G and Lamb L E Electrocardiographic findings in 122 043 individuals *Circulation* 25 947 1962
- Holzmann M Klinische Elektrokardiographie 4th edition Stuttgart 1961 Georg Thieme Verlag
- Johnson J B Ferrer M I West J R and Courmand A The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease *Circulation* 1 536 1950
- Koeffler H Die klinische Bedeutung des unvollständigen Rechtsschenkelblockes und seiner sogenannten physiologischen Variante *Z Kreislaufforsch* 50 745 1961
- Lenegre J Contribution à l'Etude des Blocs de Branche Comportant Notamment les Confrontations Électriques et Histologiques Paris 1958 J B Baillière et fils
- Lipman B S and Masse E Clinical scalar electrocardiography Chicago 1965 Year Book Medical Publishers Inc
- Lukasik S and Hurnlova L The diagnostic significance of partial right bundle branch block *Kardiologia Polska* 8 221 1965
- Masse E and Walsh T J Clinical vectorcardiography and electrocardiography Chicago 1960 Year Book Medical Publishers Inc
- Massing G K and James T N Conduction and block in the right bundle branch Real and imagined *Circulation* 45 1 1972
- Moore E N Borneau J P and Patterson D F Incomplete right bundle branch block An electrocardiographic enigma and possible misnomer *Circulation* 44 678 1971
- Penaloza D Gamboa R and Sime F Experimental right bundle branch block in the normal human heart *Am J Cardiol* 8 767 1961
- Pryor R and Blount S G The clinical significance of true left axis deviation Left intraventricular blocks *Am Heart J* 72 391 1966
- Raunio H Anttonen V M Savola P and Pyykonen L Nothing in the QRS complex in the electrocardiogram of sportsmen *Ann Clin Res* 1 5 1969
- Raunio H Rissanen V and Lampainen E Significance of a prominent S wave in leads I and V in the electrocardiograms of middle aged and elderly hospital patients *Ann Clin Res* 8 347 1976
- Raunio H Unpublished findings
- Roman G T Walsh T J and Masse E Right ventricular hypertrophy *Am J Cardiol* 7 481 1961
- Rosenbaum M B Eliazar M V and Lazzari J O The hemiblocks Florida 1970 Tampa Tracings
- Rosenbaum M B Eliazar M V Lazzari J O, Kretz A and DaRuos H O The clinical causes and mechanisms of intraventricular conduction disturbances in Advances in electrocardiography Schlant R C and Hurst J W ed New York and London 1972 Grune & Stratton Inc
- Roskamm H Reindell H Emmrich J Schmitz G Keul J and Kong H Herzvolumen und Leistungsfähigkeit bei Sportlern mit einem unvollständigen Rechtsschenkelblock im EKG *Med Klin* 57 2093 1962
- Social Insurance Institution's coronary heart disease study AL 1/1975 Helsinki 1974 Kansaneläkelaitoksen julkaisu
- Sodi Pallares D Medrano G A, Bistari A and Ponce de Leon J Deductive and polyparametric electrocardiography Instituto Nacional de Cardiología Mexico City 1970
- Young H Lieberman J and Nadas A S The normal vectorcardiogram of children *Am J Cardiol* 5 457 1960

# Evaluation of the heart rate response to the Valsalva maneuver

John H Kalbfleisch Ph D  
David F Stowe Ph D  
James J Smith MD Ph D  
Milwaukee and Wood Wisc

High work load stress testing is widely used for the detection of subjects at high risk for coronary attacks. Recently there has been increased interest in non exercise stresses such as the Valsalva maneuver which challenge the reflex control of the circulation and which may be monitored non invasively. In the Valsalva maneuver the subject ordinarily holds a predetermined airway pressure (e.g. 40 mm Hg) for a brief period such as 15 to 30 seconds. Intrathoracic and intraabdominal pressure rise, aortic flow and pressure decrease and baroreflexes are triggered. Throughout the straining phase and recovery segments of the maneuver the blood pressure (BP) and the heart rate (HR) exhibit well defined changes in normal healthy subjects. Characteristically HR is inversely related to the blood pressure events during the maneuver but patients with advanced coronary heart disease (CHD) exhibit much more sluggish responses to the Valsalva as reported by Elisberg<sup>1</sup> and ourselves. One of our recent studies indicates that in normal subjects age importantly influences the HR response to the Valsalva maneuver.

Because of the increasing evidence that HR may be a representative measure of the autonomic response to the Valsalva maneuver<sup>2</sup> we have in the present report analyzed the effect of age, posture and CHD on the Valsalva maneuver and have derived a heart rate index that may be used to assess such a response and to identify abnormal Valsalva responses.

From the Departments of Biostatistics and Physiology, Medical College of Wisconsin, Milwaukee and the Veterans Administration Center, Wood Wisc.

Received for publication Apr. 19, 1977.

Accepted for publication Aug. 2, 1977.

Reprint requests: John H. Kalbfleisch, Ph.D., Dept. of Physiology, Medical College of Wisconsin, Milwaukee Regional Medical Center, 8701 Watertown Plank Rd., Milwaukee, Wisc. 53226.

## Procedure and methods

This report is based on data obtained over a five year period on five groups of normal white male subjects and two groups of white male coronary heart disease patients subjected to a series of stress tests. Subjects with no evidence or history of cardiovascular disease who were free of hypertension, hyperglycemia, diabetes or any other obvious systemic disease and who had a negative physical exam and negative chest x-ray prior to stress testing were classified as normals. Those with typical history, ECG and symptoms consistent with CHD were classified as cardiac patients. In the 42 to 53 year old group of 11 CHD patients, 10 had angina and a positive exercise treadmill stress test and seven of these had advanced coronary disease confirmed by cardiac catheterization and angiography. The 50 to 64 year old cardiac group was composed of 11 ambulatory CHD patients all with a history of angina and (two or three vessel) coronary artery disease as documented by coronary angiography.

In all patients medication was stopped for a sufficient period prior to testing to insure non interference with functional response to the tests. Each subject performed the Valsalva maneuver by expiring forcefully and maintaining a constant airway pressure of 40 mm Hg for 15 seconds (open glottis). In some of the groups the maneuver was carried out in the supine, sitting and standing positions. Two groups (II and III, Table I) of subjects performed only the Valsalva maneuver; in the remaining the Valsalva maneuver was one of a series of five non invasive tests.

Heart rate was monitored from bipolar ECG chest leads, the ECG and airway pressure were recorded simultaneously on a Grass Polygraph (Model 5P4). Fig. 1 shows a typical instantaneous HR response of a 39 year old normal male before

Table 1 Heart rate during the 15 second Valsalva maneuver

| Group                              | Age                     | Posture  |                          | Control | Phase 1 | Phase 2  | Phase-3  | Phase-4 |
|------------------------------------|-------------------------|----------|--------------------------|---------|---------|----------|----------|---------|
| Normal Group I<br>19-26<br>Years   | Mean = 23.5<br>SD = 2.9 | Supine   | Mean<br>SEM              | 74<br>2 | 63<br>2 | 92<br>5  | 103<br>3 | 59<br>2 |
|                                    | N = 11                  | Standing | Mean<br>SEM              | 92<br>2 | 73<br>3 | 118<br>4 | 125<br>4 | 60<br>3 |
|                                    |                         |          |                          |         |         |          |          |         |
| Normal Group II<br>20-29<br>Years  | Mean = 23.1<br>SD = 1.9 | Supine   | Mean<br>SEM <sub>1</sub> | 66<br>3 | 72<br>4 | 103<br>7 | 109<br>6 | 57<br>2 |
|                                    | N = 10                  | Sitting  | Mean<br>SEM              | 74<br>4 | 73<br>5 | 110<br>8 | 114<br>8 | 53<br>2 |
|                                    |                         | Standing | Mean<br>SEM              | 82<br>4 | 85<br>5 | 118<br>7 | 121<br>8 | 58<br>4 |
| Normal Group III<br>30-39<br>Years | Mean = 34.3<br>SD = 3.2 | Supine   | Mean<br>SEM              | 65<br>3 | 75<br>5 | 95<br>8  | 102<br>8 | 50<br>2 |
|                                    | N = 9                   | Sitting  | Mean<br>SEM              | 66<br>4 | 64<br>4 | 88<br>8  | 96<br>7  | 53<br>3 |
|                                    |                         | Standing | Mean<br>SEM              | 72<br>5 | 67<br>4 | 101<br>8 | 108<br>8 | 53<br>6 |
| Normal Group IV<br>40-49<br>Years  | Mean = 45.1<br>SD = 2.9 | Sitting  | Mean<br>SEM              | 62<br>2 | 68<br>3 | 88<br>4  | 90<br>5  | 59<br>2 |
|                                    | N = 17 (30)*            |          |                          |         |         |          |          |         |
| Normal Group V<br>47-50<br>Years   | Mean = 51.4<br>SD = 3.1 | Supine   | Mean<br>SEM              | 57<br>2 | 66<br>3 | 86<br>4  | 91<br>3  | 57<br>2 |
|                                    | N = 10                  | Sitting  | Mean<br>SEM              | 60<br>2 | 63<br>2 | 87<br>2  | 94<br>2  | 57<br>2 |
|                                    |                         | Standing | Mean<br>SEM              | 69<br>2 | 73<br>3 | 97<br>2  | 101<br>2 | 61<br>4 |
| Cardiac Group I<br>42-53<br>Years  | Mean = 49.2<br>SD = 4.5 | Sitting  | Mean<br>SEM              | 68<br>3 | 70<br>4 | 92<br>5  | 91<br>6  | 69<br>3 |
|                                    | N = 11 (18)*            |          |                          |         |         |          |          |         |
| Cardiac Group II<br>50-64<br>Years | Mean = 56.8<br>SD = 4.1 | Supine   | Mean<br>SEM              | 72<br>3 | 78<br>3 | 94<br>3  | 97<br>4  | 73<br>4 |
|                                    | N = 10                  | Sitting  | Mean<br>SEM              | 77<br>4 | 78<br>3 | 94<br>3  | 97<br>4  | 77<br>4 |
|                                    |                         | Standing | Mean<br>SEM              | 84<br>4 | 86<br>3 | 105<br>3 | 108<br>3 | 81<br>4 |

In these studies most of the subjects were given two independent trials of the stress battery. Therefore the total number of trials is given in parentheses following the number of subjects.

during and after performing the Valsalva maneuver in the supine position. The HR response was scored by determining (1) the mean control HR (2) the Phase 1 HR as the lowest rate immediately after straining is initiated (3) the Phase 2 HR as the fastest rate at the end of the straining period (4) the Phase 3 HR as the maximum rate

just following release and (5) the Phase 4 HR as the slowest rate observed during the ensuing bradycardia.

Statistical analysis of the data was performed using the appropriate analysis of variance to assess the main effects of age, posture, Valsalva phases, CHD and corresponding interactions on

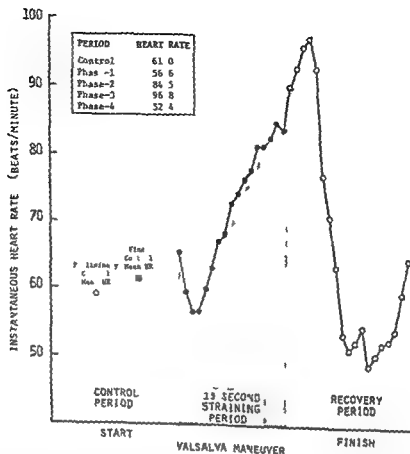


Fig 1 Instantaneous heart rate during the Valsalva maneuver for a 39-year old normal male in the supine position. Control means are average rates for 2 seconds and the control period is the two minutes preceding the test. The recovery period is about 20 seconds in duration.

the heart response. Discriminate analysis was used to help identify variables capable of distinguishing normal from CHD like responses. Multiple linear regression was employed to describe the characteristic average HR response of normals in terms of additive combinations of other easily identified variables.

## Results

The effects of age, posture and CHD on heart rate. The mean control and phase HRs during the Valsalva maneuver are shown in Table I for each of the five normal and two CHD study groups. Age and posture effects were assessed by using analysis of variance on the heart rates of the 20- to 29 year old normal Group II and the 50 to 59 year old normal Group V. Fig 2 displays the group average HRs for the Valsalva maneuver in each of three body positions in normal subjects. Results of the analysis of variance showed that significant factors were age

( $P < 0.25$ ) phases of the Valsalva maneuver ( $P < 0.01$ ) posture ( $P < 0.01$ ) and phase by age group interaction ( $P < 0.01$ ). The effect of age was evidenced by generally lower heart rates for the 47 to 56 year old normals. The posture effect was shown by the elevated HRs in the standing position with respect to supine and sitting positions ( $p < 0.01$ ). The difference between heart rates in the supine and sitting position are minimal for corresponding phases ( $1 < P < 2$ ). As expected the phases of the Valsalva maneuver elicited the most pronounced effect illustrating the progressive rise from control or Phase 1 to Phase 2 and 3 and the sharp slowdown in Phase 4. The significant phase by age group interaction results mainly from greater control to peak and greater peak to Phase 4 values in young normals.

To test for the CHD effect analysis of variance was applied to the HRs of the 47 to 56 year-old normal group and the 50 to 64 year old cardiac



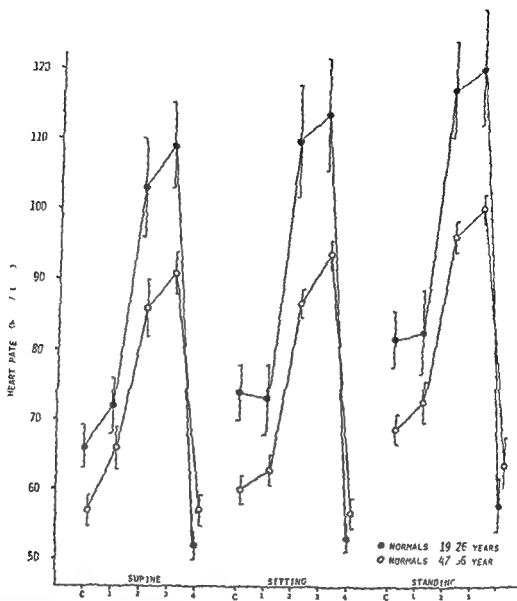


Fig 2 Control and Valsalva phase heart rates in supine, sitting and standing positions in two groups of normal men (C = control and 1 2 3 and 4 denote the phase HRs mean  $\pm$  SEM)

group Patterns of HR means for these two groups are displayed in Fig 3 Significant factors were CHD ( $P < 0.05$ ), phases of the Valsalva maneuver ( $P < 0.01$ ), and the phases by (normal cardiac) interaction The interaction effect is due to the greater rate increases (control and Phase 1 to Phase 2 and 3) and more pronounced rate decreases (Phase 2 and 3 to Phase 4) in normals than cardiac patients

From control to Phase 1 of the Valsalva maneuver a reflex HR slowing should be observed We observed this slowing in 72 per cent of the trials of young normals (Group I and II) in 48 per cent of the trials of thirty year old normals (Group III), in 35 per cent of the forty year old normal trials (Group IV) and in 23 per cent of the fifty year old normal trials (Group V) However only 19 per cent of the cardiac trials exhibited

a control to Phase 1 decrease in heart rate

Elisberg<sup>7</sup> reported that all of his normal subjects had Phase 4 HRs below control HR levels but that this occurred in only 4.5 per cent of the advanced cardiac patients In our study Phase 4 HR was less than the control HR in about 75 per cent of the normals (particularly the 19 to 26 year olds where it occurred in 90 per cent of cases) and also in 47 per cent of the cardiac patients

**Discrimination of cardiac from normal responses** As is evident from the analysis of mean HR responses the two cardiac patient groups exhibited HR patterns significantly different from the normals during the Valsalva maneuver However, to have clinical value the altered pattern of HRs in CHD should indicate discriminatory statistics that allow the identification of

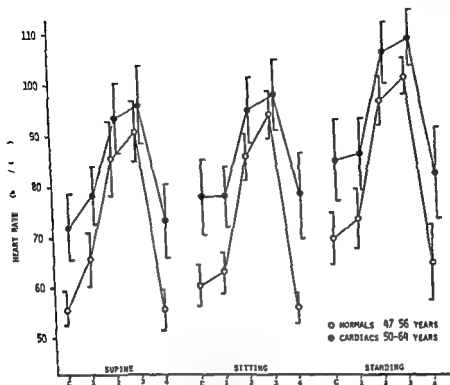


Fig 3 Control and Valsalva phase heart rates in supine sitting and standing positions in normal men and cardiac patients (C = control and 1,2,3 and 4 denote the phase HRs mean  $\pm$  SEM)

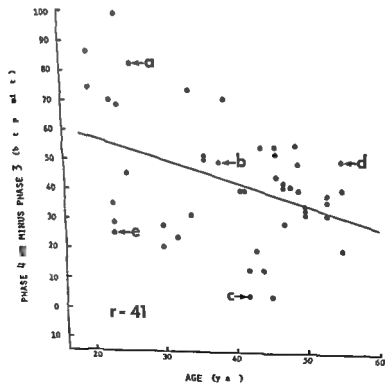


Fig 4 Relation of age and Phase 3 to Phase 4 heart rate change for normal subjects. Letters a to e identify five normal subjects in Table II

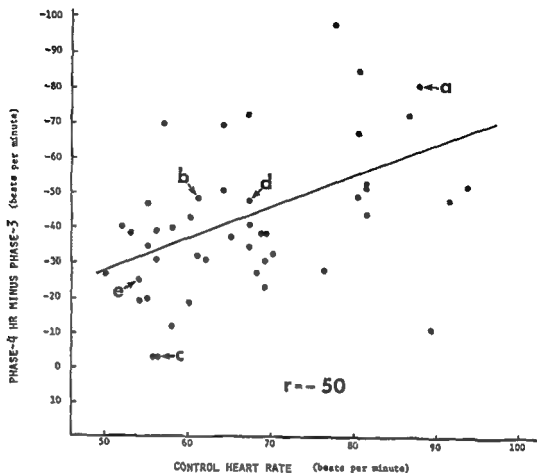


Fig 2 Relation of control heart rate and Phase 3 to Phase 4 heart rate change for normal subjects

atypical heart rate responses. The control to Phase 4 value  $\Delta(C,4)$ , suggested by Elisberg was quite reliable in discriminating advanced heart disease but in an additional group of clinically less advanced heart disease, only five of the 30 patients responded with an atypical HR change.<sup>3</sup> Among our cardiac patients only 53 per cent would be classified in the heart disease category by  $\Delta(C,4)$  and moreover about 25 per cent of our normals would fall into the heart disease group on this basis.

In an effort to identify either a single HR or combination of HR's from the pattern that can be used to distinguish the normal from the cardiac response, we applied linear discriminant analysis to the HR's of 11 pairs of age matched normals and cardiac patients. The results indicated that  $\Delta(C,4)$  was not a satisfactory measure and the best single linear discriminator was the Phase 3 to Phase 4 change in heart rate  $\Delta(3,4)$ . Addition of any other single phase HR or combination of the phase heart rates did not significantly improve discrimination over the  $\Delta(3,4)$ . This was also the case when log transformed HR's were subjected to the same analysis procedure.

**Scoring the heart rate response** Using all the HR's from Valsalva maneuvers in normal

subjects performed in the sitting position we found the  $\Delta(3,4)$  was significantly correlated with age (A), with the control HR (C) and with the Phase 3 heart rate ( $P_3$ ). These three individual relationships are illustrated in Figs 4, 5 and 6 respectively. Moreover,  $\Delta(3,4)$  can also be explained simultaneously in terms of (1) A, C and  $P_3$ , or (2) A and  $P_3$  by the multiple regression equations

$$\Delta(3,4) = 19.95 + 368A + 348C - 1.008P_3, (1)$$

$$\Delta(3,4) = 35.80 + 285A - 906P_3, (2)$$

Multiple regression analysis shows that one standard deviation unit that represents the scatter of normal responses about the average expected response is 5.75 (beats per minute) for (1) and 6.45 (beats per minute) for (2).

On this basis it is possible to score an individual's HR response to the Valsalva test by using the observed Phase 3 to Phase 4 change (denoted  $\Delta_o(3,4)$ ), A, C and  $P_3$ . If responses of healthy subjects follow a normal distribution, then standardized Valsalva scores (VS) would be

$$VS(A, C, P_3) = \frac{\Delta_o(3,4) - \Delta(3,4)}{5.75}$$

$$VS(A, P_3) = \frac{\Delta_o(3,4) - (35.8 + 285A - 906P_3)}{6.45}$$

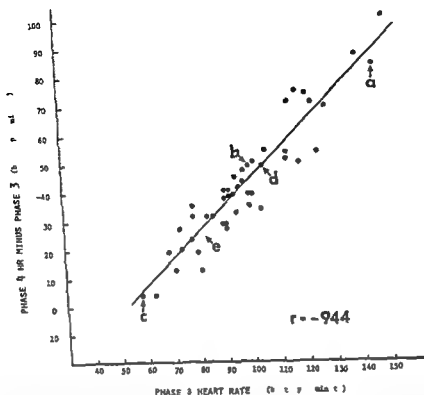


Fig 6 Relation of Phase 3 heart rate and Phase 3 to Phase 4 heart rate change for normal subjects.

Both Valsalva scores were constructed so that for normal healthy individuals the average score would be zero with about 95 per cent of the scores falling in the  $-2$  to  $+2$  range. Our 45 normals had an average  $VS(ACP_1)$  equal to  $-0.02$  ( $SD = 0.98$ ) and had an average  $VS(AP)$  of  $0.00$  ( $SD = 0.78$ ).

Diminished bradycardic responses typical of circulatory disease would have large positive Valsalva scores. The mean  $VS(ACP_1)$  of our cardiacs was  $1.53$  ( $SD = 1.84$ ) and the corresponding mean  $VS(AP)$  was  $1.99$  ( $SD = 1.92$ ). Using  $VS(ACP_1)$ , 18 of 21 cardiac patients in our series had positive Valsalva scores. Of the 18, ten scores ranged from  $1.668$  to  $5.23$  and six of these belong to the older cardiac group. Our cardiacs exhibited more dispersion in derived Valsalva scores probably because these subjects represent different stages of CHD.

Those normals and cardiac patients who were measured on two independent Valsalva tests were used to investigate the repeatability of Valsalva scores. The 40- to 49-year-old normals showed moderately high and statistically significant intraclass correlation coefficients of  $0.678$  for  $VS(ACP_1)$  and  $0.675$  for  $VS(ACP)$  ( $P < 0.1$ ). The 42- to 53-year-old cardiac group yielded

intraclass correlation coefficients of  $0.804$  for  $VS(ACP_1)$  and  $0.842$  for  $VS(ACP_1)$  ( $P < 0.1$ ). Differences in test one and test two average  $VS$ s were not statistically significant for either group. Cardiac patients showed high intraclass correlations because of a wider range of cardiac scores.

### Discussion

In most groups there were only minor differences between  $HR_{supine}$  and  $HR_{sitting}$  in the supine and sitting positions. The general effect of the upright posture was mainly to elevate both control and phase heart rates; however, this effect was complicated by the tendency of some subjects (usually those in better physical condition) to show lesser heart rate elevations during standing. This was most evident in the increased dispersion of Phase 4 heart rates during standing for the normal group (II, III, and V in Table I). These results suggest that a more valid comparative assessment of the Valsalva response can be made when performed in the supine or sitting position.

While age has not received much attention in prior Valsalva studies,<sup>2,3,7,10</sup> it is clearly an important factor in determining the response in normal males.<sup>3</sup> Our analysis showed that in older individuals there is a general tendency for

Table II Illustration of Valsalva scores for five normal subjects and three cardiac patients

|         | Age<br>(years) | Control<br>heart rate<br>(per min) | Phase 3<br>heart rate<br>(per min) | Observed<br>$\Delta(3,4)$<br>(per min) | Predicted<br>$\Delta(3,4)$<br>(per min) | VS (A,C,P) | Predicted<br>$\Delta(3,4)$<br>(per min) | VS (A,P) |
|---------|----------------|------------------------------------|------------------------------------|--|---|------------|---|----------|
| Normal  | (a) 26         | 87                                 | 146                                | -82                                    | -87.4                                   | 94         | -89.1                                   | 111      |
|         | (b) 38         | 61                                 | 100                                | -48                                    | -45.7                                   | -40        | -44.0                                   | -62      |
|         | (c) 42         | 56                                 | 58                                 | -3                                     | -3.6                                    | 10         | -4.8                                    | 29       |
|         | (d) 55         | 67                                 | 105                                | -48                                    | -42.4                                   | -98        | -43.7                                   | -66      |
|         | (e) 23         | 54                                 | 82                                 | -25                                    | -35.5                                   | 182        | -31.9                                   | 108      |
| Cardiac | 40             | 65                                 | 74                                 | -17                                    | -17.1                                   | 04         | -19.9                                   | 43       |
|         | 48             | 71                                 | 86                                 | +2                                     | -24.4                                   | 458        | -28.4                                   | 470      |
|         | 55             | 85                                 | 96                                 | -12                                    | -27.3                                   | 261        | -35.9                                   | 366      |

control HR's to decrease (Table I) but the predominant age effect is a decline in the degree of HR change between phases, particularly  $\Delta(3,4)$ . Multiple regression analysis indicated that with other factors held constant there was a 3 to 4 beat per minute reduction in heart rate response ( $\Delta(3,4)$ ) for each additional 10 years of age. This strongly implies that Valsalva responses should be judged relative to responses of healthy subjects of equivalent age. Other Valsalva studies report higher control HR's than our normals<sup>3,10</sup>, this might be due to inclusion of younger subjects or to testing conditions less suited to quiet surroundings and baseline conditions.

Our CHD patients had higher resting HR's and significantly lesser HR changes during the Valsalva. These differences were more pronounced in the 50 to 64 year age group than in the 42 to 53 year group.<sup>3</sup> Discriminate analysis indicated that the Phase 3 to Phase 4 change ( $\Delta(3,4)$ ) is the preferred discriminator between normals and cardiacs. The  $\Delta(3,4)$  difference is not seriously influenced by factors that elevate the control HR. From Phase 3 to Phase 4 the HR responds almost entirely to the dramatic changes in blood pressure which activate the autonomic circulatory control mechanisms. The autonomic response in turn is influenced by the subject's health, age and posture. Since our studies thus far have been confined to white male subjects we cannot at present evaluate the possible effect of sex or race.

The proposed Valsalva score will identify responses that deviate from the expected average normal for a given age, control HR, and Phase 3 heart rate. An abnormal response is indicated by a score of +2 or larger. With this method few normals will have large scores (high specificity). While not all CHD subjects will have large scores

a high score would theoretically suggest possible cardiac dysfunction. Valsalva scores from five normal subjects and three CHD patients are given in Table II. Normal individual 'e' has a suspiciously high VS(A,C,P), but VS(A,P), which does not use the control HR, is more indicative of a normal score. Of the three cardiacs in Table II, two had high scores and one had a quite normal score.

A high Valsalva score might be associated with circulatory abnormalities other than CHD. Using data from a Valsalva like maneuver administered to three groups in a study by Goldberg and colleagues<sup>10</sup> calculations indicate that three normals have VS(A,C,P)'s of 0.12, 0.47, and 1.83; the last is suspiciously high for a 34 year old. Three patients with mild mitral stenosis had scores of 2.53, 2.7, and 2.29. Two of these scores indicate abnormal heart rate responses to the Valsalva test. Finally a group of four patients with severe mitral stenosis (ages 22, 23, 33, and 39 years) yielded extremely high VS(A,C,P)'s of 5.52, 6.33, 6.59, and 5.70.

Abnormal Valsalva responses may also be associated with diabetic autonomic neuropathy which may affect autonomic control of the heart. In a previous study of the Valsalva response in 13 patients with this diabetic complication it was reported that reflex bradycardia was absent in seven and small in the remainder and even in the two patients with normal blood pressure over shoot, almost no heart slowing resulted.<sup>11</sup> The HR responses in these patients would result in large scores using our method of analysis. In another study of 21 diabetic outpatients (mean age 44.9 years, range 11 to 71 years) only seven of 17 successful patient trials showed normal Valsalva bradycardia.<sup>11</sup>

The HR changes during the Valsalva maneuver

are due to autonomic reflexes as evidenced by the fact that these changes may be minimized or eliminated by autonomic blockage.<sup>2</sup> The mechanisms underlying diminution of the heart rate response to the Valsalva with advanced age and heart disease are not certain but may be related to altered baroreceptor sensitivity *per se*.<sup>3</sup> Because coronary artery disease is likely to be accompanied by general systemic arteriosclerosis, this factor may contribute to reduce baroreflex sensitivity and thus result in a lesser HR effect. Alternatively, there may be diminished blood pressure changes in the Valsalva maneuver associated with hemodynamic mechanical factors such as decreased venous compliance or increased central blood volume,<sup>4</sup> either of these would diminish the usual restrictive effect of the Valsalva on cardiac filling and thus reduce the blood pressure changes presented to the baroreceptors.

It seems evident that two general mechanisms—those associated with hemodynamic factors or those associated with baroreflex responsiveness—may contribute to an abnormal response to the standard Valsalva test. Such altered responses may occur normally with advancing age or in certain cardiac or neuropathic conditions. It is important however to distinguish between the normal and the pathological. Therefore we believe that a non invasive monitoring of the heart rate response to the Valsalva maneuver and the characterization of the response in terms of age posture and Phase 3 HR may be a clinically useful technique for the early detection of heart disease.

### Summary

A study has been made of the heart rate (HR) response to the Valsalva maneuver in five different groups of normal white males and two groups of male coronary heart disease (CHD) patients using non invasive methods. By means of the analysis of variance the effects of age posture Valsalva phase and CHD on the HR response were assessed. Both age and CHD were factors that reduce the HR response. Further analysis indicated that the HR change from Phase 3 to Phase 4 in the Valsalva was the preferred discrim-

inator between normals and cardiac patients. We have derived a Valsalva score that can be used to identify HR changes that deviate from the expected average normal response for a given age control HR and Phase 3 HR. HR assessment of the Valsalva maneuver is a simple safe non invasive test. An abnormal response suggests altered functioning of hemodynamic or autonomic cardiovascular mechanisms governing HR control.

### REFERENCES

- 1 Fox J J, Crowley W P, Grace J B and Wood E H Effects of the Valsalva maneuver on blood flow in the thoracic aorta in man. *J Appl Physiol* 21: 1553, 1966.
- 2 Horner P L, Tonkin A M and Oliver J B Reflex and mechanical circulatory effects of graded Valsalva maneuvers in normal man. *J Appl Physiol* 40: 434, 1976.
- 3 Elsborg E I Heart rate response to the Valsalva maneuver as a test of circulatory integrity. *JAMA* 183: 120, 1963.
- 4 Smith J J, Tristani F E, Kalbfleisch J H, and Kotlik R J Influence of age and coronary disease on postural and Valsalva responses. *Physiologist* 19: 372, 1976.
- 5 Kalbfleisch J H, Reinke J A, Porth C J, Ebert T J and Smith J J Effect of age on circulatory response to postural and Valsalva test. *Proc Soc Exp Biol Med* 156: 100, 1977.
- 6 Smith J J, Bonin M L, Wiedmeier V T, Kalbfleisch J H and McDermott D J Cardiorespiratory response of young men to diverse circulatory stresses. *J Aerospace Med* 45: 583, 1974.
- 7 Valentuzis M E, Baker L E, Powell T The heart rate response to the Valsalva maneuver. *Med Biol Engineering* 12: 817, 1974.
- 8 Snedecor G W and Cochran W G Statistical methods. Ames, Iowa: 1969 Iowa State Univ Press 6th ed.
- 9 Goldstein R I, Bemer G D, Stamper M and Epstein S E Impairment of autonomously mediated heart rate control in patients with cardiac dysfunction. *Circ Res* 36: 571, 1975.
- 10 Goldberg H, Elsborg E I and Katz L N The effects of the Valsalva like maneuver upon the circulation in normal individuals and patients with aortic stenosis. *Circulation* 5: 8, 1972.
- 11 Lloyd Mostyn H H and Watkins P J Defective innervation of heart in diabetic autonomic neuropathy. *Br Med J* 3: 15, 1975.
- 12 Bennett J, Hoskins D J and Hampton J R Cardiovascular control in diabetes mellitus. *Brit Med J* 2: 583, 1975.
- 13 Wilkinson P L, Stone D F, Tyberg J V, and Parmley W W Pressure and flow changes during Valsalva like maneuvers in dogs following volume infusion. *Am J Physiol* 233: H 93, 1977.

# Involvement of the cardiac conducting system in panarteritis nodosa

Gaetano Thiene, M D \*  
Maralusa Valente, M D \*  
Lino Rossi, M D \*\*

Padua and Milan Italy

Heart involvement is common in panarteritis nodosa and arteritis of the extra and intramural coronary arteries with aneurysmal dilatation and thrombosis, myocardial infarction, pericarditis and hypertensive cardiopathy are the most frequently reported cardiac lesions<sup>1</sup>

Although arrhythmias, mainly from impulse formation, have been described in panarteritis, the conducting system has not been extensively studied<sup>2-5</sup> This paper reports the histopathological findings in conducting tissues in three successive, unselected cases of panarteritis nodosa

## Definition of terms and methods

The classical features of panarteritis, consisting of necrotizing angitis of the middle small sized systemic arteries<sup>1-3</sup> were observed in all three cases According to Zeek<sup>4</sup> and Allarcon Segovia and Brown true panarteritis nodosa should be distinguished from other forms of necrotizing angitis such as hypersensitivity angitis and Wegener granulomatosis, in which the inflammatory process involves the arterioles and veins as well as vessels of the pulmonary vascular bed

The histopathological investigation of the conducting system was carried out by removing the sinoatrial node and the Tawaran system from the formalin fixed hearts and processing these tissues for histology The paraffin

embedded blocks were sectioned in series retaining two sections every 20 which were stained with Haematoxylin Eosin and Elastic Van Gieson stains

## Case 1

A 11 year old girl was admitted to the Pediatric Department of our University presenting with fever, skin rash and cardiac murmur The blood pressure, normal at first, increased significantly and reached values as high as 240/140 mm Hg The nephrotic syndrome was present Hepatitis B (Australia) antigen was found in the serum, the plasma renin was increased The electrocardiogram showed left ventricular overload and a Q wave in Lead aVL (Fig 1) Systemic hypertension and renal insufficiency became more severe notwithstanding antihypertensive corticosteroid and immunosuppressive therapy and the patient died 3 months after admission from heart failure and uremia

Main postmortem findings were pulmonary edema bronchopneumonia left ventricular hypertrophy (heart weight 280 grams) healed panarteritis of the coronary arteries with aneurysms and thrombosis coarsely nodular surface of the kidneys with old thromboses of the arcuate arteries and polyvisceral healed panarteritis which however spared the spleen and the lungs

Histology of the conduction system The SA node and its main artery were free from lesions The AV node was arranged around a central artery which showed severe fibrosis destruction of the tunica elastica and luminal occlusion from an old recanalized thrombus (Fig 2) The central fibrous body showed several gaps at the fusion point between the aortic and tricuspid rings and the pars membranacea septi was markedly underdeveloped The septal tricuspid

From the Department of Pathology University of Padova Medical School, Padova and the 2nd Institute of Pathological Anatomy University of Milano Medical School Milano Italy

Received for publication Apr 25 1977

Accepted for publication Sept 26 1977

Reprint requests Gaetano Thiene MD Istituto di Anatomia e Istologia Patologica Via A Gabelli, 61 35100 Padova Italy

Department of Pathology University of Padova Medical School, Padova Italy

Second Institute of Pathological Anatomy University of Milano Medical School, Milano Italy

M.R. 6574

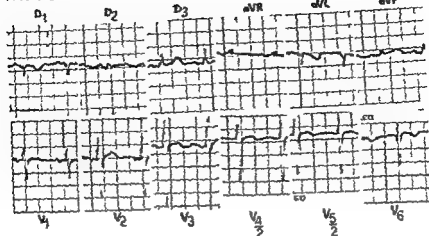


Fig 1 Case 1 The electrocardiogram recorded 5 days before death shows Q waves in II and aVL, and biventricular hypertrophy

leaflet had a high insertion and the conal septal muscle extended posteriorly. Due to the overdevelopment of the conal musculature the His bundle had an anterior intramyocardial course towards the left side and a small artery was present with aneurysmatic dilatation of the fibrotic wall (Fig 3). The bifurcation on the left side of the ventricular septum and the bundle branches were normal.

### Case 2

A 28 year old man was admitted presenting with transient amaurosis, systemic arterial hypertension and signs of congestive heart failure. Blood pressure was 210/140 mm Hg. The electrocardiogram recorded left ventricular hypertrophy (Fig 4). Australia (Au) antigen was present in the serum. The hypertension did not respond to therapy and the patient underwent two episodes of pulmonary edema. Corticosteroids were administered. Renal function deteriorated progressively. After repeated attacks of abdominal angina the patient died suddenly.

The main postmortem findings were pulmonary edema, bilateral pleural effusion, cardiomegaly with left ventricular hypertrophy, recent cardiac infarction of the right auricle and crista terminalis, coarsely nodular surface of the kidneys with obstructed intrarenal arteries, recent multiple infarctions in the spleen, kidneys, pancreas and testes. Healed polyvisceral panarteritis.

**Histology of the conduction system** The SA node centered with the nodal artery suboccluded by a partially recanalized thrombus showed extensive coagulative necrosis involving the SA nodal approaches and the contiguous ordinary atrial myocardium (Fig 5). The AV node, the His bundle and the bundle branches were normal (Fig 6). The proximal right bundle branch had an intramyocardial course. The AV node artery was supplied by several arterioles.

### Case 3

A 39 year old man was admitted to the University Hospital for sudden bilateral amaurosis. Blood pressure was 250/150 mm Hg. Renal function tests revealed severe impairment. The patient underwent recurring pulmonary edema. Hypotensive therapy succeeded in reducing systemic pressure to about 170/90 mm Hg. One year later the patient had attacks of abdominal angina. He was readmitted to Hospital with blood pressure at 230/130 mm Hg. The electrocardiogram was normal (Fig 7). Due to the worsening of abdominal conditions a laparotomy was performed and an infarction of the small intestine was detected and resected. Histological observation of the surgical specimen revealed mesenteric arteritis with occlusive thrombosis. Two days following surgery atrial arrhythmias were recorded on monitoring. On the next day the patient died suddenly.

The main postmortem findings were pulmo-





Fig 2 Case 1 A The AV node (arrows) (Elastic Van Gieson stain original magnification  $\times 12$ ) B The twin section shows bifurcation of the AV nodal artery with old thrombosis and healed panarteritis severe periarterial fibrosis and atrophy of the adjacent specific tissue (Hematoxylin and eosin stain original magnification  $\times 60$ )

nary edema heart enlargement (470 grams) with left ventricular hypertrophy moderate atherosclerosis of the subepicardial coronary arteries multiple renal infarctions, acute panarteritis including aneurysmatic dilatations involving mainly the small coronary and renal arteries

**Histology of the conduction system** The SA nodal artery and its branches exhibited acute necrotizing angitis with fibrinoid necrosis and leukocytic infiltration (Fig 8a) Aneurysmatic dilatation by rupture of the tunicae elasticae also was observed (Fig 8b) The infiltration of the arterial wall with inflammatory cells extended to the surrounding specific tissue involving also the

SA nodal approaches The AV node was normal and two small arteries within it were free from lesions (Fig 9a) The His bundle bifurcation was astride the crest of the ventricular septum (Fig 9b), and the bundle branches were normal

#### Discussion

The three cases of panarteritis reported exhibited significant lesions of the specialized conduction system of the heart due to either acute or healed angitis of the nutrient arteries of the conducting system In Case 1 healed vasculitis of the AV nodal artery was associated with extensive periarterial fibrosis and atrophy of the AV

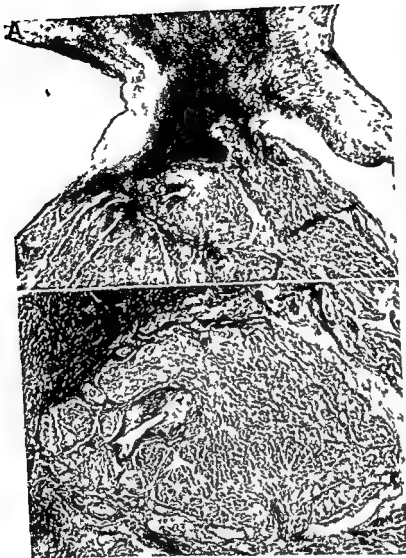


Fig 3 Case 1 A The distal tract of the common bundle below an underdeveloped membranous septum B its artery shows rupture of the tunica elastica and fibrotic dilatation (Elastic Van Gieson stain original magnifications A $\times$ 19 B $\times$ 48)

nodal specialized muscle In Case 2 arteritis of the SA nodal artery was complicated by a recent thrombosis associated with massive infarction of the SA nodal tissue and its atrial approaches. Case 3 showed acute necrotizing angitis of the SA nodal artery with fibrinoid necrosis aneurysmal dilatation of the vascular wall and phlogistic infiltration of the surrounding SA node specific tissue Hence the pathogenetic mechanisms for the conducting system lesions in panarteritis nodosa may be either ischaemic or inflammatory in nature from occlusion of the nutrient arteries or extension of the inflammation and fibrosis to the periarterial tissue respectively

James and Burk<sup>7</sup> have carried out a fundamental study of the conducting system in six cases of angitis and were the first to emphasize that since the nutrient arteries of the SA and AV nodes were ideal in size to be involved in arteritis the periarterial layout of both nodes renders them highly vulnerable to these diseases In their series they describe two cases with true panarteritis nodosa one with acute inflammatory involvement of the SA nodal artery and the other with infarction of the SA node In both patients severe atrial dysrhythmias were recorded and one patient died suddenly

Syncopal seizures probably from AV block

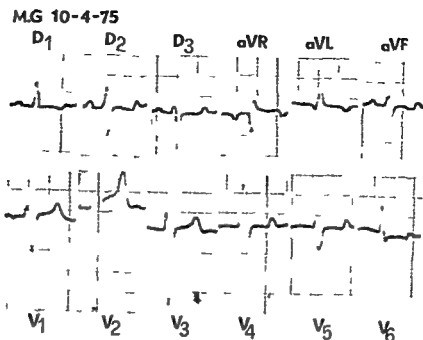


Fig 4 Case 2 Electrocardiogram left ventricular hypertrophy and prolongation of the QT segment

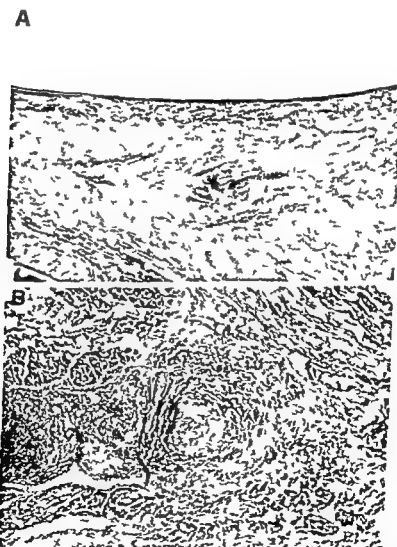


Fig 5 Case 2. A SA node with severe stenosis of the SA nodal artery (Elastic Van Gieson stain original magnification X12) B An adjacent section of the SA node shows recent thrombotic occlusion of the nodal artery and coagulative necrosis of the specific tissue (Hematoxylin and eosin stain original magnification X60)

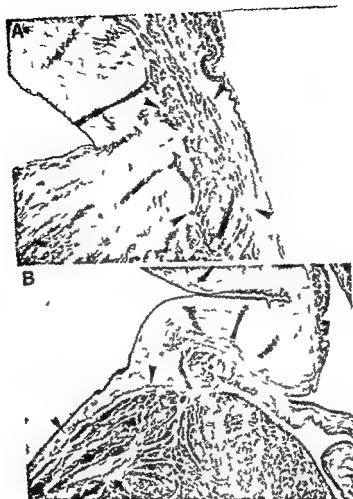


Fig 3 Case 3 The AV node (A) and the branching portion of the His bundle (B) are free from lesions (arrows) (Hematoxylin and eosin stain original magnification  $\times 19$ )

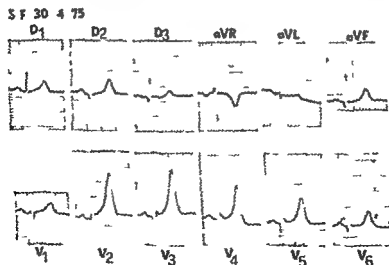


Fig 7 Case 3. The electrocardiogram without significant alterations



Fig 2 Case 3 A Acute necrotizing arteritis of the SA nodal artery with fibrinoid necrosis and leukocytic infiltration B aneurysmal dilatation and perianterial phlogistic infiltration of the specific nodal tissue (Hematoxylin and eosin stain original magnification  $\times 60$ )

were further reported by Tang and Segal<sup>1</sup> in an infant with panarteritis nodosa on histological examination subocclusion of the AV nodal artery with perianterial fibrosis was observed as in Case 1 of our series

Our observations endorse the foregoing reports concerning the significant association of panarteritis with conducting system disease due to involvement of the nutrient arteries With regard to the apparent clinicopathological discrepancy in our first two patients who failed to show the expected electrocardiographic manifestations of damage to cardiac specialized tissue it is known

that the early clinical signs of diseased sinoatrial and/or atrioventricular activation are at times very elusive It has been claimed that in apparently normal individuals the only evidence of Sick Sinus Syndrome often consists of brief and transient arrhythmias whose recognition may require cardiac monitoring over periods of 24 hours or more<sup>2</sup> Indeed only our third case underwent cardiac monitoring and happened to exhibit atrial dysrhythmias that had completely escaped recording by the standard surface electrocardiograms Sudden death in this case and in patient No 2 may also be tentatively explained by the

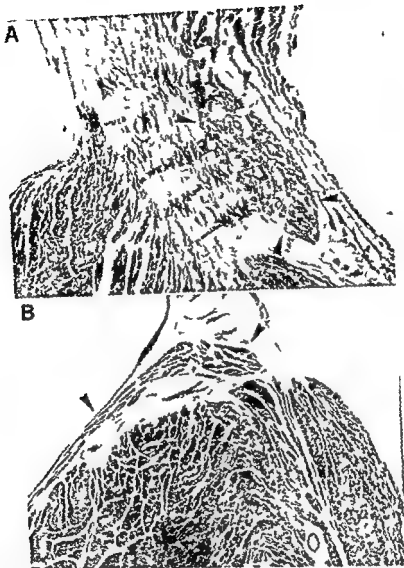


Fig 9 Case 3. A The distal AV node and B the branching portion of the His bundle free from lesions (arrowhead) (Hematoxylin and eosin stain original magnification  $\times 19$ )

fatal outcome of a cardiac arrest and/or arrhythmic attack complicating SA or AV conduction impairments.

Our cases of panarteritis nodosa were not selected on the basis of electrocardiographic evidence of arrhythmias. In our opinion the postmortem finding of pathologic lesions of the specific cardiac tissue in all three hearts supports the view that panarteritis nodosa involves the conducting system often enough to represent on pathophysiological and clinical ground a major impending threat to the patients irrespective of existence of related rhythm disorders on occasional surface electrocardiograms and routine medical

examinations. Prolonged cardiac monitoring and appropriate controls by catheter recording and stimulation techniques are highly recommended in these patients whenever possible for early detection and prevention of life threatening arrhythmias from altered impulse formations and conduction.

#### Summary

Histopathological observations on the conduction system of the heart were carried out in three cases of panarteritis nodosa. This specialized tissue was involved in each case secondary to ischemia and/or periarterial extension of the

inflammatory process affecting the nutrient arteries of the conducting system. The high risk of disturbances in impulse formation and conduction in patients with periarthritis is emphasized as well as the need for appropriate clinical investigation (protracted cardiac monitoring and control by catheter recording and stimulation) in order to secure early detection and prevention of life threatening arrhythmias.

The authors wish to express gratitude to Paolo Veronese Giuseppe Ravenna Agostino Leorin and Alessandra Turco for their assistance. Mrs Patricia Segato assisted in the preparation of the manuscript.

# REFERENCES

- 1 Holsinger D R Osmundson P J and Edwards J E  
The heart in periarthritis nodosa *Circulation* 25 610  
1962
- 2 James T N and Burk R E Pathology of the cardiac  
conduction system in polyarteritis nodosa *Arch Intern  
Med* 117 561 1966
- 3 Tang P H L and Segal A J *Polyarteritis nodosa of  
infancy fatal late complication* *J A M A* 217 1656,  
1971
- 4 Kussmaul A and Maier R I *Über eine bisher nicht  
beschriebene eigenthümliche arterienkrankung (Periar-  
teritis nodosa)* *Deutsch Ark klin Med* 1 484 1866.
- 5 Arkin A *A clinical and pathological study of periar-  
teritis nodosa* *Am J Pathol* 6 401 1930
- 6 Zeek P M *Periarthritis nodosa and other forms of  
necrotizing angitis* *N Engl J Med* 248 764 1953
- 7 Alarcon Segovia D and Brown A L *Classification  
and etiologic aspects of necrotizing angitides* *Mayo Clin  
Proc* 39 205 1964
- 8 Editorial *Sick Sinus Syndrome* *Br Med J* 1 4 1977

## Vagal tone significance of electrophysiologic findings and clinical course in symptomatic sinus node dysfunction

Jochen Thormann M D

Franz Schwarz M D

Roland Ensslen M D

Michael Sesto M D

Bad Nauheim West Germany

The role of vagal tone in symptomatic sinus node dysfunction is subject to much controversy.<sup>1-3</sup> Some authors assume that massage of the carotid sinus in the presence of sick sinus syndrome (SSS) causes excessive slowing of the heart since it is thought that marked organic disease of the sinus node predisposes excessive responses to vagotonic maneuvers. However, relative unresponsiveness to atropine was found in SSS in a majority of cases studied by others,<sup>4-6</sup> suggesting sinus node dysfunction independent of the carotid sinus reflex. In a previous study we found no evidence of SSS in patients with hypersensitive carotid sinus reflex (HCSR) and we assumed that symptomatic sinus node dysfunction was caused by excessive response to vagal stimulation.

The indication for pacer application in HCSR and SSS is often based on severe clinical symptomatology rather than on the specific test results. A systematic evaluation of the literature regarding the course of HCSR and SSS is lacking and yet information of this sort could be useful for therapeutic considerations such as pacer application. The present study was intended to (1) investigate vagal influence on HCSR and SSS, (2) ascertain if the combination of HCSR + SSS found in the same patient might at least in part be based on an uniform physiologic concept, (3) try to classify or correlate symptomatic severity of both syndromes and electrophysiologic findings as regards their clinical

implication and (4) analyze the course of SSS by restudying a group of patients.

### Patients and methods

The population under study consisted of 186 symptomatic patients with complaints of dizziness, syncope or inability to concentrate or a combination of these symptoms. Forty patients were female, 146 were male. Their mean age was  $58.3 \pm 11.4$  years. Cerebrovascular disease, acute myocardial ischemia, aortic stenosis, third degree AV block and subclavian steal syndrome were all excluded as possible causes for syncope and dizziness. The patients were divided into four groups according to the results of electrophysiologic testing: group I consisting of 103 patients with evidence of HCSR showed a maximum P-P interval (P-P vs R-R,  $p > 0.05$ )  $> 3$  sec following carotid sinus pressure (CSP max).<sup>7</sup> Thirty three patients with a combination of both HCSR + SSS (CSRT max  $\geq 560$  msec, CSP max  $\geq 3$  sec respectively)<sup>8,9</sup> made up group II. Group III consisted of 30 patients with evidence of isolated SSS. Group IV included 20 patients who according to complete testing showed no evidence of either HCSR or SSS. Clinical data, symptoms and ECG findings of the four groups are listed in Table I. 16.3  $\pm$  10.5 months after the initial investigation, another 16 patients with SSS were restudied in order to analyze the natural course of this syndrome.

Prior to study a complete medical history and physical examination, chest x-ray, ECG, as well as informed consent were obtained in all patients. At the time of study all cardioactive medication

From the Klinik für Innere Medizin, Bad Nauheim West Germany.

Received for publication June 13, 1977.

Accepted for publication December 18, 1977.

Reprint requests: Jochen Thormann, M.D., Benkertstrasse 6-8, D-6350 Bad Nauheim, West Germany.



Table I Clinical data of the 186 patients investigated

|                      |                               | Group I<br>(HCSR) | Group II<br>(HCSR + SSS) | Group III<br>(SSS) | Group IV<br>(Control) |
|----------------------|-------------------------------|-------------------|--------------------------|--------------------|-----------------------|
| Patients             | No of cases                   | 103               | 33                       | 30                 | 20                    |
|                      | Age (years mean)              | 59.9              | 60.6                     | 55.3               | 57.3                  |
|                      | Female patients               | 15%               | 27%                      | 46%                | 15%                   |
|                      | Male patients                 | 85%               | 73%                      | 54%                | 85%                   |
| Symptoms             | Syncope                       | 14%               | 9%                       | 18%                | 0                     |
|                      | Dizziness                     | 25%               | 27%                      | 36%                | 35%                   |
|                      | Syncope + dizziness           | 41%               | 45%                      | 42%                | 0                     |
|                      | Others                        | 20%               | 19%                      | 4%                 | 65%                   |
|                      | Total                         | 100%              | 100%                     | 100%               | 100%                  |
| Additional diseases  | Congenital heart disease      | 2%                | 6%                       | 11%                | 0                     |
|                      | Rheumatic heart disease       | 9%                | 3%                       | 11%                | 10%                   |
|                      | Coronary heart disease        | 37%               | 42%                      | 39%                | 34%                   |
|                      | Hypertension                  | 36%               | 33%                      | 14%                | 35%                   |
|                      | Chronic pulmonary disease     | 9%                | 3%                       | 7%                 | 18%                   |
|                      | Others                        | 7%                | 13%                      | 18%                | 3%                    |
|                      | Total                         | 100%              | 100%                     | 100%               | 100%                  |
| Routine ECG Findings | S A block (arrest)            | 15%               | 39%                      | 63%                | 5%                    |
|                      | PACs                          | 6%                | 24%                      | 43%                | 5%                    |
|                      | AF (intermittent)             | 21%               | 27%                      | 25%                | 10%                   |
|                      | Atrial flutter (intermittent) | 2%                | 16%                      | 19%                | 0                     |
|                      | PAT (with block)              | 8%                | 21%                      | 14%                | 0                     |
|                      | A V 1° block                  | 14%               | 12%                      | 10%                | 5%                    |
|                      | PVCs                          | 18%               | 24%                      | 26%                | 15%                   |
|                      | RBBB LBBB LAD                 | 36%               | 27%                      | 16%                | 28%                   |

had been discontinued for an interval exceeding three drug half lives. All patients were studied in the resting nonsedated, postabsorptive state. Two transvenous catheter electrodes were positioned high on the lateral wall of the right atrium. One was used for bipolar stimulation of the atrium, the other for recording atrial electrograms which were registered by a multichannel ink writing system simultaneously with surface ECG leads or by using His bundle recordings.<sup>24</sup> In only a few cases were multichannel surface lead registrations used alone. After control recording, a 3 sec CSP during sinus rhythm was repeatedly applied to the left and right carotid sinus in turn with 1 minute pauses between tests. Following a ten minute stabilization period five series of atrial stimulation (AST) with rates ranging 80 to 200 bpm and a 2 msec constant current pulse at approximately two times atrial diastolic threshold were applied for 1 minute each (overdrive).<sup>25</sup> Atrial electrograms and/or His bundle recordings were subsequently registered for at least 1 minute after the interruption of AST (overdrive suppression).<sup>26</sup> The investigation was repeated 3 minutes

after the intravenous application of atropine 1 mg. Restudy after 16 months in 16 patients who had meanwhile undergone therapeutic pacemaker application, required the temporary suppression of the impulse emission of the implanted unit. This was accomplished by electrical chest wall stimulation during testing.<sup>27</sup>

### Calculations

The control P-P interval was averaged from 30 beats. P-P intervals were measured from the CSP ECGs up to 30 sec following CSP. The maximal CSP result was used for evaluation (CSP max). Maximal corrected sinus node recovery time (CSRT max)<sup>28</sup> was calculated as maximal P-P interval after AST (= maximal sinus node recovery time) minus mean P-P interval at rest. Abnormalities of the first post pacing cycle (CSRT max  $\geq$  560 msec)<sup>29</sup> and secondary pauses<sup>30,31</sup> were identified and accepted as diagnostic criterion for SSS. Cases with atrial premature depolarizations or junctional escape beats with atrial capture were considered, provided they occurred at least 1.4 sec following postdrive

Table II Summary of electrophysiologic findings (mean  $\pm$  SEM)

| Groups     | Number of cases | Age (years) | Before atropine   |                   |                            | After atropine    |              |                           |                            |
|------------|-----------------|-------------|-------------------|-------------------|----------------------------|-------------------|--------------|---------------------------|----------------------------|
|            |                 |             | HR ( $\delta$ pm) | CSP (msec)        | CSRT <sub>max</sub> (msec) | HR ( $\delta$ pm) | HR delta (%) | CSP <sub>max</sub> (msec) | CSRT <sub>max</sub> (msec) |
| HCSR       | 103             | 59.8        | 59.0              | 5.96              | 249.3                      | 79.7              | 33.8         | 1328                      | 231                        |
| (I)        |                 | $\pm 1.0$   | $\pm 0.9$         | $\pm 1.79$        | $\pm 15.5$                 | $\pm 1.5$         | $\pm 2.1$    | $\pm 4^*$                 | $\pm 13$                   |
| HCSR + SSS | 33              | 60.6        | 58.4              | 5.16 <sup>a</sup> | 348.8                      | 75.6              | 27.9         | 1270                      | 3015                       |
| (II)       |                 | $\pm 1.8$   | $\pm 2.0$         | $\pm 2.31$        | $\pm 26.7$                 | $\pm 2.6$         | $\pm 2.6$    | $\pm 184$                 | $\pm 553$                  |
| SSS        | 30              | 55.3        | 58.9              | 1690              | 3603                       | 74.7              | 28.3         | 1233                      | 3818                       |
| (III)      |                 | $\pm 2.5$   | $\pm 7.5$         | $\pm 1.1$         | $\pm 40.2$                 | $\pm 2.8$         | $\pm 7.9$    | $\pm 84$                  | $\pm 455$                  |
| Controls   | 20              | 57.3        | 66.8              | 1.70              | 962.0                      | 81.4              | 33.1         | 1182                      | 234.0                      |
| (IV)       |                 | $\pm 2.4$   | $\pm 1.4$         | $\pm 1.10$        | $\pm 9.2$                  | $\pm 2.8$         | $\pm 4.1$    | $\pm 49$                  | $\pm 8.3$                  |

\*  $p < 0.05$ \*  $p < 0.01$  vs Controls\*  $p < 0.001$  in 11 instances.

cardiac standstill. Statistical evaluation was carried out using the *t* test for paired and unpaired data.

### Results

**A Clinic.** Syncope without dizziness was found in 9 to 18 per cent of the patients in the three groups with symptomatic sinus node dysfunction (Table I). The combination of both syncope and dizziness was rather frequent in all three groups (41 to 45 per cent). Dizziness without syncope was present in 25 to 36 per cent of the patients studied. Several patients in all groups complained of an inability to concentrate only tiredness or apathy. Most patients in group IV suffered either slight dizziness off and on or an inability to concentrate and forgetfulness.

As regards additional diseases coronary heart disease (37 to 42 per cent) and hypertension (14 to 36 per cent) were maximally represented in all three groups followed by chronic pulmonary diseases (3 to 9 per cent) and congenital heart disease (2 to 11 per cent).

Routine ECG registrations in all three groups (Table I) revealed a maximal occurrence of S A block and/or S A arrest (15 to 80 per cent) followed by intraventricular conduction disturbances (16 to 36 per cent) and premature atrial contraction (6 to 43 per cent) intermittent atrial fibrillation (21 to 27 per cent) and premature ventricular contractions (18 to 26 per cent). Paroxysmal atrial tachycardias (8 to 21 per cent) intermittent atrial flutter (2 to 19 per cent) and first degree AV block (10 to 14 per cent) were observed less frequently in all three groups. There

was a prevalent occurrence of S A block and premature atrial contractions in group III, intraventricular conduction disturbances in group I and atrial flutter and paroxysmal atrial tachycardia in both groups II and III compared to the rest of the groups.

**B Electrophysiology.** The results of electrophysiologic testing are presented in Table II. Groups I to III showed no difference in age compared to controls ( $p > 0.05$ ). Heart rate at rest was slower in group I ( $p < 0.001$ ), group II ( $p < 0.01$ ) and group III ( $p < 0.01$ ) compared to controls. CSP was used to separate group I and group II from group III and was 5.3 sec for group I and 5.2 sec for group II. Group III had a CSP max value of 1.7 sec which is within the normal range ( $p > 0.05$ ). CSRT which was used to separate group II and III from group I was 0.25 sec in group I, considered normal ( $p > 0.05$ ). Group II had an average CSRT of 3.5 sec, group III of 3.6 sec.

**C Atropine study.** After atropine heart rate at rest was 79 bpm in group I, 76 bpm in group II and 75 bpm in group III. All values for heart rate were significantly slower than those of controls (see Table II). CSP max after atropine was no longer prolonged in groups I to III compared to controls ( $p > 0.05$ ). CSRT max was 0.23 sec in group I ( $p < 0.05$  vs controls) but 3.0 and 3.8 sec in groups II and III ( $p < 0.001$ ). Heart rate increased by 34 per cent in group I, 28 per cent in group II and 28 per cent in group III. All these changes were not different from those of controls ( $p > 0.05$ ).

**D Clinical correlations (Fig. 1).** No significant

Table I Clinical data of the 186 patients investigated

|                      |                               | Group I<br>(HCSR) | Group II<br>(HCSR + SSS) | Group III<br>(SSS) | Group IV<br>(Control) |
|----------------------|-------------------------------|-------------------|--------------------------|--------------------|-----------------------|
| Patients             | No of cases                   | 103               | 33                       | 30                 | 20                    |
|                      | Age (years mean)              | 59.9              | 60.6                     | 55.3               | 57.3                  |
|                      | Female patients               | 15%               | 27%                      | 46%                | 15%                   |
|                      | Male patients                 | 85%               | 73%                      | 54%                | 85%                   |
| Symptoms             | Syncope                       | 14%               | 9%                       | 18%                | 0                     |
|                      | Dizziness                     | 25%               | 27%                      | 36%                | 35%                   |
|                      | Syncope + dizziness           | 41%               | 45%                      | 42%                | 0                     |
|                      | Others                        | 20%               | 19%                      | 4%                 | 65%                   |
|                      | Total                         | 100%              | 100%                     | 100%               | 100%                  |
| Additional diseases  | Congenital heart disease      | 2%                | 6%                       | 11%                | 0                     |
|                      | Rheumatic heart disease       | 9%                | 3%                       | 11%                | 10%                   |
|                      | Coronary heart disease        | 37%               | 42%                      | 39%                | 34%                   |
|                      | Hypertension                  | 36%               | 33%                      | 14%                | 30%                   |
|                      | Chronic pulmonary disease     | 9%                | 3%                       | 7%                 | 18%                   |
|                      | Others                        | 7%                | 13%                      | 18%                | 3%                    |
|                      | Total                         | 100%              | 100%                     | 100%               | 100%                  |
| Routine ECG Findings | S A block (arrest)            | 15%               | 39%                      | 63%                | 5%                    |
|                      | PACs                          | 6%                | 24%                      | 43%                | 5%                    |
|                      | AF (intermittent)             | 21%               | 27%                      | 25%                | 10%                   |
|                      | Atrial flutter (intermittent) | 2%                | 15%                      | 19%                | 0                     |
|                      | PAT (with block)              | 8%                | 21%                      | 14%                | 0                     |
|                      | A V 1° block                  | 14%               | 12%                      | 10%                | 5%                    |
|                      | PVCs                          | 18%               | 24%                      | 26%                | 15%                   |
|                      | RBBB LBBB LAD                 | 36%               | 27%                      | 16%                | 28%                   |

had been discontinued for an interval exceeding three drug half lives. All patients were studied in the resting nonsedated postabsorptive state. Two transvenous catheter electrodes were positioned high on the lateral wall of the right atrium. One was used for bipolar stimulation of the atrium; the other for recording atrial electrograms which were registered by a multichannel ink writing system simultaneously with surface ECG leads or by using His bundle recordings.<sup>22</sup> In only a few cases were multichannel surface lead registrations used alone. After control recording a 3 sec CSP during sinus rhythm was repeatedly applied to the left and right carotid sinus in turn with 1 minute pauses between tests. Following a ten minute stabilization period, five series of atrial stimulation (AST) with rates ranging 80 to 200 bpm and a 2 msec constant current pulse at approximately two times atrial diastolic threshold were applied for 1 minute each (overdrive).<sup>23</sup> Atrial electrograms and/or His bundle recordings were subsequently registered for at least 1 minute after the interruption of AST (overdrive suppression).<sup>24</sup> The investigation was repeated 2 minutes

after the intravenous application of atropine 1 mg. Restudy after 16 months in 16 patients, who had meanwhile undergone therapeutic pacemaker application, required the temporary suppression of the impulse emission of the implanted unit. This was accomplished by electrical chest wall stimulation during testing.<sup>25</sup>

#### Calculations

The control P-P interval was averaged from 30 beats. P-P intervals were measured from the CSP ECGs up to 30 sec following CSP. The maximal CSP result was used for evaluation (CSP max). Maximal corrected sinus node recovery time (CSRT max)<sup>26</sup> was calculated as maximal P-P interval after AST (= maximal sinus node recovery time) minus mean P-P interval at rest. Abnormalities of the first post pacing cycle (CSRT max  $\geq$  560 msec)<sup>27</sup> and secondary pauses<sup>28,29</sup> were identified and accepted as diagnostic criterion for SSS. Cases with atrial premature depolarizations or junctional escape beats with atrial capture were considered, provided they occurred at least 1.4 sec following postdrive

Table II Summary of electrophysiologic findings (mean  $\pm$  SEM)

| Groups          | Number of cases | Age (years)    | Before atropine |                           |                            | After atropine |                |                           |                            |
|-----------------|-----------------|----------------|-----------------|---------------------------|----------------------------|----------------|----------------|---------------------------|----------------------------|
|                 |                 |                | HR (bpm)        | CSP <sub>max</sub> (msec) | CSRT <sub>max</sub> (msec) | HR (bpm)       | HR delta (°)   | CSP <sub>max</sub> (msec) | CSRT <sub>max</sub> (msec) |
| HCSR (I)        | 103             | 59.9 $\pm$ 1.0 | 59.2 $\pm$ 0.9  | 5.96 $\pm$ 1.9            | 249.3 $\pm$ 15.5           | 79.7 $\pm$ 1.5 | 33.8 $\pm$ 2.1 | 1328 $\pm$ 42             | 231 $\pm$ 13               |
| HCSR + SSS (II) | 33              | 60.6 $\pm$ 1.6 | 58.4 $\pm$ 2.0  | 5.62 $\pm$ 2.31           | 248.8 $\pm$ 26.7           | 75.6 $\pm$ 2.6 | 27.9 $\pm$ 2.6 | 1270 $\pm$ 184            | 2015 $\pm$ 553             |
| SSS (III)       | 30              | 55.3 $\pm$ 2.5 | 58.9 $\pm$ 2.5  | 1690 $\pm$ 17             | 3603 $\pm$ 409             | 74.7 $\pm$ 9.8 | 28.3 $\pm$ 9.9 | 1233 $\pm$ 84             | 3818 $\pm$ 455             |
| Controls (IV)   | 20              | 57.3 $\pm$ 2.4 | 66.8 $\pm$ 1.4  | 1.0 $\pm$ 110             | 267.0 $\pm$ 9.2            | 87.4 $\pm$ 2.8 | 33.1 $\pm$ 4.1 | 1182 $\pm$ 49             | 234.0 $\pm$ 8.3            |

\*  $p < 0.05$ \*  $p < 0.01$   $P$  sinus vs Controls\*  $p < 0.001$  in all studies etc.

cardiac standstill. Statistical evaluation was carried out using the  $t$  test for paired and unpaired data.

### Results

**A Clinic.** Syncope without dizziness was found in 9 to 18 per cent of the patients in the three groups with symptomatic sinus node dysfunction (Table I). The combination of both syncope and dizziness was rather frequent in all three groups (41 to 45 per cent). Dizziness without syncope was present in 25 to 36 per cent of the patients studied. Several patients in all groups complained of an inability to concentrate, only tiredness or apathy. Most patients in group IV suffered either slight dizziness off and on or an inability to concentrate and forgetfulness.

As regards additional diseases, coronary heart disease (37 to 42 per cent) and hypertension (14 to 36 per cent) were maximally represented in all three groups followed by chronic pulmonary diseases (3 to 9 per cent) and congenital heart disease (2 to 11 per cent).

Routine ECG registrations in all three groups (Table I) revealed a maximal occurrence of S A block and/or S A arrest (15 to 63 per cent) followed by intraventricular conduction disturbances (16 to 36 per cent) and premature atrial contraction (6 to 43 per cent), intermittent atrial fibrillation (21 to 27 per cent) and premature ventricular contractions (18 to 26 per cent). Paroxysmal atrial tachycardias (8 to 21 per cent), intermittent atrial flutter (2 to 19 per cent) and first degree AV block (10 to 14 per cent) were observed less frequently in all three groups. There

was a prevalent occurrence of S A block and premature atrial contractions in group III, intraventricular conduction disturbances in group I and atrial flutter and paroxysmal atrial tachycardia in both groups II and III compared to the rest of the groups.

**B Electrophysiology.** The results of electrophysiologic testing are presented in Table II. Groups I to III showed no difference in age compared to controls ( $p > 0.05$ ). Heart rate at rest was slower in group I ( $p < 0.001$ ), group II ( $p < 0.01$ ) and group III ( $p < 0.01$ ) compared to controls. CSP was used to separate group I and group II from group III and was 5.3 sec for group I and 5.2 sec for group II. Group III had a CSP max value of 1.7 sec which is within the normal range ( $p > 0.05$ ). CSRT which was used to separate group II and III from group I was 0.25 sec in group I, considered normal ( $p > 0.05$ ). Group II had an average CSRT of 3.5 sec, group III of 3.6 sec.

**C Atropine study.** After atropine, heart rate at rest was 79 bpm in group I, 76 bpm in group II and 75 bpm in group III. All values for heart rate were significantly slower than those of controls (see Table II). CSP max after atropine was no longer prolonged in groups I to III compared to controls ( $p > 0.05$ ). CSRT max was 0.23 sec in group I ( $p < 0.05$  vs controls) but 3.0 and 3.8 sec in groups II and III ( $p < 0.001$ ). Heart rate increased by 74 per cent in group I, 28 per cent in group II and 28 per cent in group III. All these changes were not different from those of controls ( $p > 0.05$ ).

**D Clinical correlations (Fig 1).** No significant

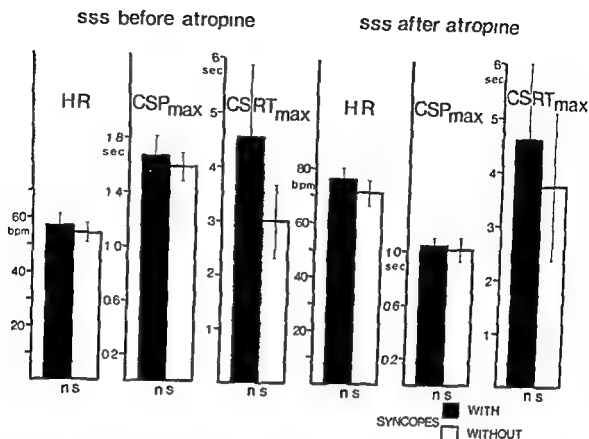


Fig 1 The graph demonstrates no significant differences in SSS patients exemplary for groups I to III between electrophysiologic data in patients with syncope (black columns) compared to patients without syncope (light columns). This indicates that electrophysiologic testing establishes diagnoses but fails to predict severe clinical symptoms in symptomatic sinus node dysfunction. Mean  $\pm$  SEM for all measurements.

differences were found for heart rate, CSP max and CSRT max, both before and after atropine ( $p > 0.05$ ) when for each of groups I to III, values of patients with histories of syncope versus those without were separately compared. This is graphically exemplified for group III (Fig 1).

**E Restudy of SSS** A restudy of 16 additional cases of SSS (cases Nos 2, 6, 14, and 15 had HCSR as well) was carried out 16 months after the initial study and pacemaker application. There were no significant differences in heart rate, CSP max and CSRT max, either before or after atropine when the results of the first and the second study were compared. No differences could be ascertained for patients with histories of syncope versus those without when heart rate, CSP max and CSRT max were compared 16 months after the initial study. The values (mean  $\pm$  SEM) versus those 16  $\pm$  26 months later (before atropine) were as follows: HR ( $58 \pm 3$  bpm vs  $54 \pm 3$  bpm,  $p > 0.05$ ), CSP max ( $2.0 \pm 0.4$  sec vs  $1.9 \pm 0.3$  sec,  $p > 0.05$ ) and CSRT max ( $4.6 \pm 1.2$  sec vs  $5.8 \pm 1.4$  sec,  $p > 0.05$ ). The values versus those 16  $\pm$  26 months later (after atropine) were as follows: HR

( $74 \pm 4$  bpm vs  $70 \pm 3$  bpm,  $p > 0.05$ ), CSP max ( $1.1 \pm 0.08$  sec vs  $1.1 \pm 0.06$  sec,  $p > 0.05$ ) and CSRT max ( $5.6 \pm 1.5$  sec vs  $6.2 \pm 1.4$  sec,  $p > 0.05$ ).

## Discussion

**A Methods** Some methodological problems need discussion. Although many investigative protocols for the study of SSS use the technique of His bundle electrocardiography,<sup>9,10,11,21,22,23,24</sup> diagnostically sound information can be obtained by the use of atrial electrograms and simultaneous multiple surface ECG leads<sup>25,26,27</sup> such as were employed in the majority of cases in this study. However, since a considerable number of patients with the Sick Sinus Syndrome have disease of the distal conduction system, the use of a His bundle electrocardiogram is useful in detecting such patients.

The CSRT values appear long in this study. Since methods of calculating CSRT vary, the average lengths of prolonged CSRT in the literature vary as well, at about 2.8 to 5 cm. CSRT is long when spontaneous postpacing atrial depolarization of sinus origin and/or late retrograde

junctional activity are accepted as sinus node recovery<sup>18, 21, 22</sup> and CSRT is shorter ( $< 3$  sec) when any ectopic postpacing atrial deflection is also taken as sinus recovery<sup>7, 8, 9, 17</sup>. Since direct measurement of sinus node activity is not available the actual sinus recovery might of course have occurred any time between a late postdrive junctional escape beat and an even later occurring P of ectopic origin and have just been suppressed by retrograde activity.

It should be considered that only a limited number of patients with SSS have an abnormal CSRT borne out by previous studies<sup>1, 2, 27, 28</sup> in which prolonged CSRT in 56 per cent (35 to 93 per cent) of the patients with symptomatic sinus node disease was found. Such false negative responses of atrial tachypacing have been attributed to the failure of consistent depolarization of the sinus node by the paced atrial beats due to entrance block<sup>16, 17</sup>. To minimize such errors we followed recommended techniques that included assessing prior to diagnostic AST sequences the reset of S A node by an initial run of atrial pacing at rates lower than the intrinsic sinus rate at rest using six sequences of different AST rates in overdrive testing to increase the chance of stimuli penetrating the atrium and the S A node<sup>1, 27</sup> should an optimal rate for penetration of temporary entrance block exist<sup>6, 7</sup> repeating all AST runs after the application of atropine (thought to abolish entrance block)<sup>17</sup>. However our group II and III patients who were selected on grounds of pathologic CSRT alone might still not be representative for all patients with symptomatic sinus node disease.

**B Electrophysiologic data.** In contrast to group II (HCSR + SSS) isolated SSS patients (group III) did not show positive CSP reaction. Some authors found positive CSP response the major manifestation of sinus node dysfunction in 13 per cent of their cases with sinus node disease and a poor atropine response independent of the carotid sinus reflex was suggested as evidence of sinus node dysfunction. This view is not supported by our findings. Heart rate was found to be identical in all three groups but significantly slower compared to controls (Table II). After atropine the relative increase of heart rate for all groups was about 31 per cent and was identical to that of controls ( $p > 0.05$ ). However evaluated absolutely heart rate of all groups was again significantly lower compared to controls

( $p < 0.05$ ). Atropine normalized all CSP induced asystoles ( $p > 0.05$ ) but left unchanged pathologically increased CSRT max values. In our opinion vagal activity alone cannot adequately explain such findings. We conclude that an increased vagal tone is primarily responsible for the CSP induced bradycardias and asystoles. While an organic S A node destruction and/or disturbance of sinoatrial conduction should be postulated for group II (HCSR + SSS) and group III (isolated SSS) a decreased catecholamine response might be discussed for the group with isolated HCSR. With appropriate testing HCSR and SSS are apparently separable entities and the combination of both syndromes occurs rather frequently. All three groups in our study present slower resting heart rates which could be but one hallmark for symptomatic sinus node disease. To what degree the increased vagal tone is responsible for this bradycardia remains open to further investigation.

**C Correlation of symptoms and electrophysiology.** In our population of symptomatic patients with sinus node dysfunction about 50 per cent complained of syncopal attacks. This rather high percentage is similar to that (50 per cent  $\pm$  14 per cent) found by previous investigators<sup>6, 7, 3, 13, 16</sup>. When patients in this study with syncope were compared to patients without syncope no differences within the three groups between heart rate, duration of CSP max and CSRT max results before and after atropine were found. We consider this to be a most important result since we found that patients with severe symptoms cannot be separated from patients with mild symptoms using electrophysiologic testing. This implies that spontaneous arrhythmic disturbances causing severe symptoms can not be predicted from careful electrophysiologic studies. The clinical dilemma of indication of pacemaker application cannot be solved by comparison of electrophysiologic data.

Attempts to classify SSS according to degrees of severity take different approaches in different investigations and they are far from being systematic. Apparently pacemaker treated series are composed of patients with severe symptoms and may not be representative. All attempts thus far to identify subgroups of SSS have proven statistically unreliable<sup>3, 6, 13, 16, 27, 32, 33, 34</sup> as did ours in the present study. This implies that in each case questionable symptoms need to be

meticulously tested and pacemaker therapy applied liberally, since, although death is more likely due to secondary events rather than the syncopal attack, virtually even asymptomatic patients with pathologic test results can become the victim of their first syncope.<sup>43</sup>

The time interval between the occurrence of apparently minor symptoms and syncope in patients with sinus node dysfunction may extend beyond 5 years. This observation agrees with other investigations.<sup>6, 15, 18, 31, 33</sup> However, reports regarding the natural history, prognosis and follow up in SSS are rare in the literature and usually consist of mere prognostic observations without actual electrophysiologic restudies in sinus node dysfunction. In this study, which is we believe the first of its kind, there was no significant change in CSRT max, CSP max and heart rate before and after atropine application within a period of 16 months between the initial study and the restudy of 16 cases with SSS. This implies poor prognosis in SSS and confirms the results of Gupta and associates<sup>18</sup> and Narula and colleagues<sup>15</sup> who reported CSRT was reproducible after 7.5 months (6 months respectively) in one of their patients.

### Summary

The relation of hypersensitive carotid sinus syndrome (HCSR) to sick sinus syndrome (SSS) is not clear. Vagal role, relevance of electrophysiologic testing and the natural course of both syndromes are ill defined. In 186 symptomatic patients resting heart rate (HR), carotid sinus pressure results (CSP) and corrected sinus node recovery time (CSRT) were determined before and after atropine (A). According to test results 102 patients had HCSR (group I), 33 had HCSR + SSS (group II), 30 patients had isolated SSS (group III) and 20 served as control (group IV). HR below 60 bpm in groups I to III and lower than controls ( $p < 0.01$ ) rose after A by approximately 31 per cent in groups I to IV. This indicates predominant vagal tone and establishes that rate response to A is unreliable as a diagnostic test for groups I to III. CSP normalized after A but CSRT remained unchanged ( $p > 0.05$ ) which implies increased vagal tone in HCSR but destructive affection of the SA node in SSS. Bradyarrhythmia, SA block, supraventricular tachyarrhythmias and the combination of dizzi-

ness and syncope served as diagnostic clues for HCSR or SSS in a limited number of patients. CSP and CSRT separated HCSR from SSS but failed to predict syncope in groups I to III ( $p > 0.05$ ) and thereby cannot aid the indication for pacemaker application. SSS test results remained unchanged over 16 months showing an unfavorable prognosis. We conclude that HCSR and SSS although frequently occurring together are entities made separate by specific testing which, however, fails to aid in therapeutic decision making. Vagal tone plays but one role in HCSR and SSS and electrophysiologic pathology of SSS does not improve in its course.

### REFERENCES

1. Agruss N S, Rosin E Y, Adolph H J and Fowler N O. Significance of chronic sinus bradycardia in elderly people. *Circulation* 46:924, 1972.
2. Allen H N, Mandel W J, Obayashi K and Hayakawa H. Sick sinus syndrome. Alterations in sinus and AV nodal function by changes in autonomic tone. *Circulation* 49 and 50 (Suppl. III) 213, 1974.
3. Aroesty J M, Cohen S I and Morkin F. Bradycardia-tachycardia syndrome: results in twenty-eight patients treated by combined pharmacologic therapy and pacemaker implantation. *Chest* 66:257, 1974.
4. Beshour T, Hemb H and Wickramakran H. An unusual effect of atropine on overdrive suppression. *Circulation* 48:911, 1973.
5. Behar V, Strauss H C, Benditt D G, Scheinman M M and Wallace A G. Analysis of secondary pauses following termination of rapid atrial pacing in man. *Circulation* 53 and 54 (Suppl. II) 127, 1976.
6. Burchfield R I, Menefee E E and Bryant G D. N. Disease of the sinoatrial node associated with bradycardia, asystole, syncope and paroxysmal atrial fibrillation. *Circulation* 16:20, 1957.
7. Breithardt G, Seipel L and Loogen F. Sinus node recovery time and calculated sinoatrial conduction time in normal subjects and patients with sinus node dysfunction. *Circulation* 55:43, 1977.
8. Crook B, Kitson D, McMahon M and Jewitt D. Indirect measurement of sinoatrial conduction time in patients with sinoatrial disease and in controls. *Br Heart J* 39:771, 1977.
9. Dhingra R C, Amat y Leon F, Wyndham C, Dines P, Wu D, Miller R H and Rosen K M. Electrophysiologic effects of atropine on sinus node and atrium in patients with sinus nodal dysfunction. *Am J Cardiol* 38:848, 1976.
10. Dhingra R C, Amat y Leon F, Wyndham C, Dines P, Wu D, Jouget J M and Rosen K M. Electrophysiologic effects of atropine on human sinus node and atrium. *Am J Cardiol* 38:429, 1976.
11. Dighton D H. Sinus bradycardia: Autonomic influences and clinical assessment. *Br Heart J* 36:791, 1974.
12. Easley R M, Jr and Goldstein S. Sinoatrial syncope. *Am J Med* 50:166, 1971.
13. Eckberg D L, Fletcher C F and Braunwald F. Mechanism of prolongation of the R-R interval with

- electrical stimulation of the carotid sinus nerves in man  
*Circ Res* 30 131 1972
- 4 Ernst F and Shaw I Sinus bradycardia *Br Heart J*  
33 742, 1971
- 5 Ferrer I The sick sinus syndrome *Circulation* 47 635  
1973
- 6 Coldreyer B H and Damato A N sino atrial node  
entrance block, *Circulation* 44 789 1971
- 7 Gupta P H, Lichtstein E, Chadda K D and Badier F  
Appraisal of sinus nodal recovery time in patients with  
sick sinus syndrome *Am J Cardiol* 34 265 1974
- 8 Jordan J, Yamaguchi I and Mandel W J Studies on  
the mechanism of sinus node dysfunction in the sick  
sinus syndrome *Circulation* 54 (Suppl II) II 230  
1976
- 9 Kaplan B M, Langendorf R, Lev M and Puck A.  
Tachycardia-bradycardia syndrome (so-called sick si-  
nus syndrome): Pathology, mechanism and treatment  
*Am J Cardiol* 31 497 1973
- 10 Kulbertus H E, De Leval Rutten F, Mary L, and  
Casters P Sinus node recovery time in the elderly *Br*  
*Heart J* 37 420 1975
- 11 Lange G Action of driving stimuli from intrinsic and  
extrinsic sources on in situ cardiac pacemaker tissues  
*Circ Res* 17 449 1965
- 12 Lee C H, Cohen L S and Cannon D S Limitations  
of sinoatrial recovery time in assessing sinus node  
dysfunction *Circulation* 52 (Suppl II) II 12 1975
- 13 Lu R H, Lange G and McBrooks C Factors  
controlling pacemaker action in cells of the sinoatrial  
node *Circ Res* 17 460 1965
- 14 Mandel W J, Hayakawa H, Allen H N, Danzig R,  
and Kermaier H Assessment of sinus node function in  
patients with the sick sinus syndrome *Circulation*  
45 761 1972
- 15 Mandel W, Hayakawa, H, Danzig R and Marrus  
H S Evaluation of sino atrial node function in man by  
overdrive suppression *Circulation* 44 59 1971
- 16 Moss A J and Davis R J Brady tachy syndrome  
*Progr Cardiovasc Dis* 16 439 1974
- 17 Natolia O M, Samet P and Javier R P Significance of  
the sinus node recovery time *Circulation* 45 140 1972
- 18 Raamussen K Chronic sinoatrial heart block *Am*  
*Heart J* 81 38, 1971
- 19 Ruffel J A, Bigger J T and Giordano E G V  
Paradoxical prolongation of sinus nodal recovery time  
after atropine in the sick sinus syndrome *Am J Cardiol*  
38 98 1975
- 20 Rios J C, Bashour T, Cheng T O and Motomiya T  
Atrial pacing in sick sinus syndrome *Circulation* 48  
(Suppl II) II 211 1973
- 21 Rokseth R and Hatle L Prospective study on the  
occurrence and management of chronic sinoatrial  
disease with follow up *Br Heart J* 36 587 1974
- 22 Rosen A M, Loeb H E, Sinno M Z, Rahmtoola S  
H and Gunnar R M Cardiac conduction in patients  
with asymptomatic sinus node disease *Circulation* 43 836  
1971
- 23 Rubenstein J J, Schulman C L, Yurchak P M and  
DeSanctis R W Clinical spectrum of the sick  
syndrome *Circulation* 46 1977
- 24 Scarpa W J The sick sinus syndrome *Am Heart J*  
92 648 1976
- 25 Schettmann, M M, Evans, G T, Abbot J, Peters R,  
Wallace A G and Strauss H C Electrophysiologic  
testing of patients with sinoatrial block and sinus pauses  
*Circulation* 53 and 54 (Suppl II) II 231 1976
- 26 Scherlag B J, Lau S H, Helfant H H, Berkowitz W,  
D Stein E and Damato A M Catheter technique for  
recording His bundle activity in man *Circulation* 39 13  
1969
- 27 Schwarz F, Thormann J and Zimmermann H Vagal  
influence on sinus rate and AV conduction in hypersen-  
sitive carotid sinus reflex and sick sinus syndrome  
*Schweiz. Med Wschr* 105 240 1975
- 28 Strauss, H C and Bigger J T Jr Slowed conduction  
block and reentry in perinatal fibers, *Circulation* 44  
(Suppl II) II 74 1971
- 29 Strauss, H C, Gilbert M, Svenson R H, Miller H C  
and Wallace H C Electrophysiologic effects of propra-  
nolol on sinus node function in patients with sinus node  
dysfunction *Circulation* 54 457 1976
- 30 Thomas, J E Hyperactive carotid sinus reflex and  
carotid sinus syncope *Mayo Clin Proc* 44 127 1969
- 31 Thormann J and Schwarz F Vagal role and pace-  
maker indication in hypersensitive carotid sinus reflex  
*Europ J Cardiol* 3/1 47 1975
- 32 Thormann J, Schwarz, F and Ensslen R Evaluation  
of implanted faulty demand pacemakers by magnet  
waving and electrical chest wall stimulation. A report of  
clinical experience *Europ J Cardiol* 5/2 139 1977
- 33 Tazuka J, Hattori M and Tanahashi, Y Fifth Inter-  
national Symposium on Cardiac Pacing Tokyo March  
14 18 1976 abstracts p 90 No 131
- 34 Vera P, Mason D T, Awan N A, Miller R R,  
Jehzen D, Tonkon M J and Vismara, L A Improve-  
ment of symptoms in patients with sick sinus syndrome  
by spontaneous development of stable atrial fibrillation  
*Br Heart J* 39 160 1977
- 35 Wan, S H, Lee G S and Toh C C S The sick sinus  
syndrome. A study of 15 cases, *Br Heart J* 34 947  
1972



# Differences in metal content of the heart muscle in death from ischemic heart disease

Barbara Chipperfield, M A, Ph D

J R Chipperfield, M A Ph D

Hull England

The increased death rate from ischemic heart disease in soft water areas suggested that the mineral salt concentration in the drinking water affected the death rate from ischemic heart disease, and that there was a specific effect on the heart muscle.<sup>1</sup> Since the increased death rate in soft water areas seems to be due to an increase in sudden deaths, the metal content of the heart muscle in those dying suddenly from ischemic heart disease is of particular interest.

We have shown that there is a significant decrease in magnesium concentration in the heart muscle of those dying suddenly from ischemic heart disease.<sup>2</sup> This was confirmed by Behr and Burton<sup>3</sup> who found that although there was a decrease in magnesium in the heart muscle in those dying suddenly from heart disease there was no decrease in chronic heart disease or in the skeletal muscle of those dying suddenly. Anderson and co workers<sup>4</sup> have confirmed the decrease in magnesium in death from heart disease. They also found a significant increase in the calcium concentration and a decrease in the copper concentration in the heart muscle of those dying from ischemic heart disease but no significant differences in the concentrations of zinc, chromium, cadmium and lead.

We have reported separately some work on the concentrations of silicon and aluminum in the heart muscle of those dying suddenly from ischemic heart disease.<sup>5</sup> This report compares the concentrations of several metals of interest in the

heart muscle from three different groups: one control group of patients with apparently normal heart muscle, a group of late heart deaths, and a sudden heart death group. The causes of death in the normal control group included accidental and suicide deaths, pneumonia and some deaths from cancer. We have shown that there was no significant difference in magnesium concentration of accident and suicide deaths as compared to those from sudden and chronic illness unrelated to heart disease.<sup>1</sup> The late death group represented chronic heart disease and these were defined as patients who had suffered a coronary thrombosis and died more than three months later. The sudden death group were defined as in our previous report.<sup>1</sup>

## Materials and methods

Samples of left ventricle were taken at necropsy and in the deaths from ischemic heart disease were from uninfarcted areas of the ventricle. All the sudden death samples and some of the normal control group came from the Hull City Mortuary; they were stored at 4° C for 1 to 3 days then stored at -20° C until they were prepared for analysis. All the late death samples and the other normal control samples came from the Hull Royal Infirmary and were stored at -20° C immediately after necropsy. There was no significant difference between the normal samples from these two different sources.

Samples of heart muscle were wet ashed as described previously.<sup>1</sup> The sulphuric acid which was present in solutions prepared by the wet ash method interfered in analyses for calcium. For calcium analyses samples of ventricular muscle (ca 5 Gm) in platinum crucibles were dried to constant weight at 100° C and were then ashed in a muffle furnace at 450° C. The ash was dissolved

From the Departments of Biochemistry and Chemistry, The University of Hull, England.

This work was supported by a Project Grant from the Medical Research Council.

Received for publication Sept. 13, 1977.

Accepted for publication Oct. 1, 1977.

Reprint requests: Dr B Chipperfield, Department of Biochemistry, University of Hull, Hull, HU6 7RA, England.

Table 1 Metal concentrations in heart muscle

|                   |  | Sudden heart death |      |        | Late heart death |      |        | Normal controls |      |        |
|-------------------|--|--------------------|------|--------|------------------|------|--------|-----------------|------|--------|
|                   |  | All                | Male | Female | All              | Male | Female | All             | Male | Female |
|                   |  | 154                | 10   | 109    | 173              | 170  | 175    | 186             | 181  | 190    |
| Magnesium         | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) |                    |      |        |                  |      |        |                 |      |        |
|                   | SD   | 27                 | 29   | 22     | 17               | 20   | 10     | 20              | 28   | 22     |
|                   | Number                                     | 59                 | 43   | 16     | 72               | 9    | 13     | 158             | 72   | 66     |
| Calcium           | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 57.0               | 56.9 | 57.4   | 43.1             | 39.8 | 45.3   | 39.0            | 42.5 | 36.1   |
|                   | SD   | 26.0               | 26.2 | 26.2   | 15.8             | 6.5  | 19.9   | 22.9            | 25.2 | 20.7   |
|                   | Number                                     | 59                 | 43   | 16     | 72               | 9    | 13     | 129             | 57   | 72     |
| Sodium            | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 906                | 805  | 937    | 947              | 903  | 942    | 889             | 903  | 901    |
|                   | SD   | 328                | 346  | 209    | 223              | 227  | 229    | 222             | 255  | 190    |
|                   | Number                                     | 59                 | 43   | 16     | 72               | 9    | 13     | 158             | 72   | 66     |
| Potassium         | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 180                | 1490 | 1830   | 2130             | 2160 | 2110   | 2080            | 1870 | 2250   |
|                   | SD   | 60                 | 690  | 530    | 370              | 40   | 300    | 00              | 680  | 680    |
|                   | Number                                     | 36                 | 27   | 9      | 22               | 9    | 13     | 158             | 72   | 66     |
| Iron              | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 385                | 376  | 416    | 486              | 514  | 466    | 468             | 407  | 478    |
|                   | SD   | 110                | 109  | 108    | 81               | 93   | 68     | 96              | 110  | 81     |
|                   | Number                                     | 36                 | 28   | 9      | 22               | 9    | 13     | 158             | 72   | 66     |
| Copper            | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 311                | 308  | 319    | 284              | 277  | 288    | 332             | 330  | 330    |
|                   | SD   | 044                | 048  | 049    | 036              | 037  | 038    | 066             | 063  | 063    |
|                   | Number                                     | 31                 | 23   | 8      | 22               | 9    | 13     | 56              | 31   | 25     |
| Manganese         | Conc ( $\mu\text{g}/\text{Gm}$ wet weight) | 0.96               | 0.97 | 0.91   | 0.6              | 0.72 | 0.80   | 1.07            | 1.15 | 0.96   |
|                   | SD   | 0.16               | 0.19 | 0.15   | 0.23             | 0.21 | 0.25   | 0.31            | 0.36 | 0.20   |
|                   | Number                                     | 31                 | 23   | 8      | 22               | 9    | 13     | 56              | 31   | 25     |
| Magnesium/calcium | Ratio                                      | 3.60               | 3.60 | 3.58   | 4.40             | 4.47 | 4.47   | 6.13            | 5.72 | 6.46   |
|                   | SD   | 2.35               | 46   | 2.11   | 1.32             | 1.12 | 1.49   | 2.64            | 2.71 | 2.06   |
|                   | Number                                     | 59                 | 43   | 16     | 72               | 9    | 13     | 199             | 57   | 72     |
| Age               | Mean                                       | 66.5               | 64.3 | 26     | 0.7              | 64.3 | 52     | 58.1            | 55.4 | 60.4   |
|                   | SD   | 9.9                | 9.6  | 8.1    | 11.8             | 10.3 | 9.5    | 20.7            | 20.5 | 20.1   |
|                   | Number                                     | 59                 | 43   | 16     | 72               | 9    | 13     | 158             | 72   | 66     |

in the minimum quantity of hydrochloric acid. Appropriate quantities of the wet ash (Mg, Na, K, Fe, Cu, Mn) or dry ash (Mg, Ca, Na, K, Fe, Cu, Mn) solutions were analyzed by atomic absorption spectrophotometry using a Perkin Elmer Model 305B spectrophotometer with an air/acetylene flame. Analyses for magnesium, sodium, potassium, manganese and copper of solutions prepared by wet ashing and dry ashing the same sample gave excellent agreement. Analyses for iron on wet ashed samples were corrected for the blank reading found for this element.

## Results

The concentrations of lithium, lead, chromium, cobalt, strontium, cadmium and mercury in our solutions were so low that they were not measurable by flame atomic absorption techniques. Table 1 gives the concentrations (in  $\mu\text{g}/\text{Gm}$  wet weight) of magnesium, calcium, sodium, potassium, iron, manganese and copper in our three groups and Fig. 1 indicates the percentage difference from the normal control group in the two heart death groups for all these elements and for the magnesium/calcium ratio.

There was a highly significant ( $t = 8.14$ )

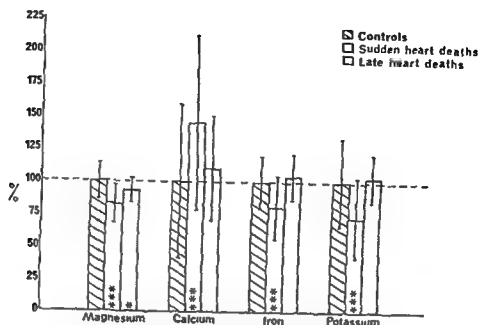


Fig 1 Comparative metal concentrations of heart muscle (controls = 100 per cent) Bar lines show standard deviations probably significant  $0.05 > P > 0.01$  significant  $0.01 > P > 0.001$  highly significant  $0.001 > P$

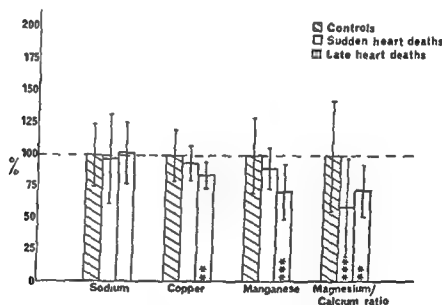


Fig 1 ■ For legend see above

decrease in the magnesium concentration in the sudden death group as expected from earlier work. This difference was still highly significant ( $t = 5.33$ ) when normal males were compared with males from the sudden heart death group and when normal females were compared with females of the sudden heart death group ( $t = 5.14$ ). There was a much smaller decrease in magnesium in the late death group which was only significant at the 5 per cent level ( $t = 2.30$ ) and was only probably significant in females ( $t = 2.34$ ) when the sexes were considered separately.

There was no significant difference between the calcium concentrations of the normal and late death groups but the sudden death group showed a highly significant ( $t = 4.81$ ) increase in calcium. The difference in females was also highly significant ( $t = 3.55$ ) but in males the difference was only significant at the 1 per cent level ( $t = 2.77$ ).

For both potassium and iron concentrations there was no significant difference between the normal and late death groups but a highly significant decrease in the sudden death group ( $t = 4.10$  for potassium,  $4.58$  for iron). The potas

sium in normal males was significantly ( $t = 3.50$ ) lower than in normal females. When males and females were considered separately the decrease in potassium in the sudden death group was only probably significant for the males ( $t = 2.42$ ) and not significant for the females ( $t = 1.81$ ). The decrease in iron concentration was still significant when males and females were considered separately, though  $t$  was higher for the males (3.32) than for the females (2.10).

The results for copper and manganese concentrations were very different from those for the other elements. The slight decrease in both elements in the sudden death group was not statistically significant but the late death group showed a highly significant decrease in manganese ( $t = 4.24$ ) and a significant difference in the copper concentration ( $t = 3.21$ ). When males and females were considered separately the decreased manganese in the males was significant at the 1 per cent level ( $t = 3.39$ ) and the other comparisons were all probably significant.

There was no significant difference in the magnesium/potassium ratio between the groups but a highly significant decrease in the magnesium/calcium ratio of the sudden death group compared with the normals ( $t = 6.30$ ). The decreased magnesium/calcium ratio in the sudden death group was highly significant for both males ( $t = 4.02$ ) and females ( $t = 4.18$ ) compared separately. This ratio was also significantly decreased in the late death group compared with the normal group ( $t = 3.00$ ) but was only significant in females ( $t = 2.84$ ) when the sexes were compared separately.

The differences between the sudden death and late death groups were highly significant for the potassium concentration, significant for the magnesium, iron, manganese and copper concentrations and probably significant for the calcium concentration.

Measurements of the water content of some of the heart muscle samples indicated that there was no significant difference in the water content of the heart muscle from the three groups so that these wet weight comparisons are also valid as indications of the relative concentrations per gram dry weight.

Statistical analysis indicated that there was no significant variation with age for the concentrations of any of the elements. Histograms of the

results indicated that the distributions were reasonably normal and Wilcoxon Mann-Whitney significance tests gave similar results to the  $t$  tests.

## Discussion

A general feature of our results is the similarity of the late heart death group to the normal control group apart from the significant decreases in manganese and copper concentrations and the magnesium/calcium ratio in the late heart death group. This suggests that other factors being equal the concentrations of some metals in the heart muscle may be important in deciding whether a patient survives a coronary thrombosis.

In the sudden heart death group there were significant decreases in the concentration of magnesium, potassium and iron and a significant increase in the concentration of calcium. The decrease in magnesium confirms the results from earlier studies.<sup>1,2</sup> Seelig<sup>3</sup> has suggested that the Western diet is deficient in magnesium and that lack of magnesium may be a cause of the increased death rate from ischemic heart disease in soft water areas<sup>4,5</sup> and Bradshaw and Dean<sup>6</sup> have suggested that a prospective study of those regularly taking magnesium salts should be carried out to show whether magnesium has a specific protective effect in ischemic heart disease. Anderson and colleagues<sup>7</sup> found that the magnesium concentration of normal heart muscle was slightly lower in soft water areas of Canada compared with hard water areas whereas our comparison of English hard and soft water areas showed the reverse.<sup>12</sup> We suggested that possibly the magnesium/potassium ratio which was lower in the soft water area might be important in susceptibility to death from ischemic heart disease. In the present survey however there is no significant difference in magnesium/potassium ratio between the sudden death group and the normal group.

Previous studies of both animals and men have usually found a decrease in potassium accompanying the decreased magnesium in hearts affected by ischemic heart disease and related conditions. Our earlier investigation<sup>1</sup> showed a slight but not statistically significant decrease in potassium concentration in the hearts of those dying suddenly from ischemic heart disease and

in this larger study the potassium concentration in the sudden heart deaths was significantly reduced. There was a negative correlation between the cardiovascular mortality rate in South Wales and the potassium content of the drinking water, but Elwood, Abernethy, and Morton<sup>13</sup> considered that this was negligible as compared with the correlation with the calcium content of the drinking water. In comparing normal hearts from Hull and Burnley, we found that there was a significant increase in the potassium concentration in the heart muscle samples from the soft water area (Burnley),<sup>12</sup> which makes it unlikely that any increased death rate in soft water areas is directly related to potassium metabolism.

Calcium also seems to be ruled out as the 'water factor' by these results. Our sudden death group, like the Canadian heart deaths, had a significantly increased calcium concentration, which makes it unlikely that the decreased calcium content of soft water is the factor increasing heart deaths. It is not likely that this higher calcium is due to deposition of calcium salts in atheromatous plaques, since there was no significant increase in the calcium in our late death group where such deposits might also be expected. Since there are established interrelations between calcium and magnesium,<sup>14</sup> it is possible that, as suggested by Anderson and associates,<sup>5</sup> the increased calcium in the sudden heart deaths may be secondary to the decrease in magnesium concentration. Calculations on Anderson and colleagues' data<sup>5</sup> show that there is a highly significant decrease in the magnesium/calcium ratio in the heart deaths in the Canadian survey, like the decrease in this ratio we report here. In the soft water areas the magnesium/calcium ratio in the heart deaths was 2.47 while in the accident cases it was 4.10 ( $t = 7.45$ ), in the hard water areas the ratio in heart deaths was 2.47 and the accident death ratio was 4.23 ( $t = 5.04$ ). The slight decrease in the accident deaths in the soft water area was not statistically significant, but it is in the direction one would expect if this ratio change contributed to the increased death rate in soft water areas. This ratio may vary in different populations as the means in our investigation are nearly 50 per cent greater than the values for the corresponding Canadian groups.

The decreased iron concentration in the sudden

heart death group is unexpected. The iron will be almost entirely bound in the heme groups of myoglobin and the cytochromes.<sup>15</sup> These proteins are most unlikely to leak out of cells after death as might occur with the small cations, so the iron decreases must have occurred before death. Decreases in the concentration of these heme proteins will decrease the cell's capacity to react with oxygen and thus the rate of production of adenosine triphosphate will be lower. A lower capacity to produce adenosine triphosphate may be a great disadvantage in conditions of oxygen shortage after a myocardial infarction.

We found a decrease in copper concentration for the late heart death group but not for the sudden heart death group. Anderson and co-workers<sup>1</sup> found a decrease in copper concentration in the heart muscle of those dying from ischemic heart disease. About 85 per cent of their heart deaths occurred less than 24 hours after the first symptoms so their patients could be considered as intermediate between our sudden and late death groups. Severe copper deficiency has been associated with effects on the heart in cows and pigs.<sup>16</sup> Our results suggest that copper deficiency is not important in those dying suddenly from ischemic heart disease, but may be important to those who survive the initial myocardial infarction.

Although we found a decrease in manganese in the late deaths, the total concentration of this element is very small. Manganese can normally replace magnesium *in vitro* as an activator of enzymes acting on adenosine triphosphate so the decrease in manganese may add to the harmful effects of the slight decrease in magnesium in the late deaths. Cardiovascular mortality has been shown to have a positive association with manganese in water,<sup>17</sup> however, which suggests that manganese may have a harmful effect on the heart.

These results suggest that the factor most likely to increase the death rate in soft water areas may be a decrease in the magnesium/calcium ratio as these two cations are vitally important in the control of muscular contraction.<sup>18</sup> The iron concentration in the heart was not measured in the Canadian study and Elwood, Abernethy, and Morton<sup>13</sup> did not report on the iron concentrations in their water samples. It is possible that a decrease in the iron in the heart muscle in soft water areas might also

contribute to the increased death rate. Preliminary results<sup>4</sup> suggest that possible toxic effects from aluminum are also worth investigation.

The sudden heart death group showed significant decreases in the concentration of magnesium, iron and potassium. Decreases in magnesium, iron and potassium have recently been established in Kwashiorkor.<sup>14</sup> Magnesium deficiency has been particularly associated with the electrocardiographic changes in Kwashiorkor<sup>15</sup> and in alcoholic heart disease.<sup>16</sup> Sudden death from ischemic heart disease may be another result of empty calorie malnutrition. Diets which are high in fats and refined carbohydrates will probably be low in mineral salts.<sup>17</sup> It is therefore possible that the harmful effect of Western diets on ischemic heart disease rates is not due to the increase in saturated fats, cholesterol or sucrose but to a deficiency of mineral salts. This deficiency could lead to the decreased concentration of several vital metals we have observed in those dying suddenly from ischemic heart disease.

### Summary

In a group of patients dying suddenly from ischemic heart disease the uninfarcted heart muscle contained significantly lower concentrations of magnesium, iron and potassium and a significantly higher concentration of calcium than the heart muscle from a group of normal controls and a group of patients dying more than three months after a coronary thrombosis. The late death group had significantly lower concentrations of manganese and copper than the normal group and a slight decrease in magnesium concentration which was probably significant. There was no significant difference in the sodium concentration between the three groups.

The results are discussed in relation to the increased death rate from ischemic heart disease in areas with soft drinking water and possible dietary deficiencies in mineral salts.

We thank Mrs. Y. P. Thompson for her skilful technical help, the Coroner, pathologists and mortuary staff at the Hull City Mortuary and Hull Royal Infirmary for help in collection of samples and Mr. A. G. Memon for statistical help.

### REFERENCES

- 1 Crawford M D., Gardner M J., and Morris J N. Cardiovascular disease and the mineral content of drinking water. *Br Med Bul.* 27 21 1971.
- 2 Anderson T W, Le Riche W H and MacKay J S. Sudden death and ischemic heart disease. Correlation with hardness of local water supply. *N Engl J Med* 280 805 1969.
- 3 Chipperfield B., and Chipperfield J R. Heart muscle magnesium, potassium and zinc concentrations after sudden death from heart disease. *Lancet* 2 293 1973.
- 4 Behr G and Burton P. Heart muscle magnesium. *Lancet* 2 40 1973.
- 5 Anderson T W, Neri L C, Schreiber G B., Talbot, F D F and Zdrojewski A. Ischemic heart disease, water hardness and myocardial magnesium. *Can Med Assoc J* 113 199 1975.
- 6 Chipperfield B, Chipperfield J R and Bower N R. Silicon and aluminum in heart deaths. *Lancet* 1 705 1977.
- 7 Chipperfield B, Chipperfield J R, Behr G and Burton P. Magnesium in heart muscle. *Lancet* 1 1354 1976.
- 8 Seelig M S. The requirement of magnesium by the normal adult. *Am J Clin Nutr* 14 342 1964.
- 9 Seelig M S. Myocardial loss of functional magnesium. II. In cardiomyopathies of diverse etiology. *Recent Adv Struct Metab* 1 676 1979.
- 10 Seelig M S and Heggstad H A. Magnesium interrelationships in ischemic heart disease. *Am J Clin Nutr* 27 59 1974.
- 11 Bradshaw J E and Dean G. Epimol salts and coronary heart disease. *Fractionator* 216 673 1978.
- 12 Chipperfield B, Chipperfield J R., Behr G and Burton P. Magnesium and potassium content of normal heart muscle in areas of hard and soft water. *Lancet* 1 121 1976.
- 13 Elwood P C, Abernethy M and Morton M. Mortality in adults and trace elements in water. *Lancet* 2 14 0 1974.
- 14 Irving J T. Calcium and phosphorus metabolism. New York 1973. Academic Press.
- 15 Jacobs A and Worwood M., editors. Iron in biochemistry and medicine. London 1974. Academic Press.
- 16 Adelstein E J and Vallee B L. In Mineral metabolism. Vol. 2B, edited by C L. Comar and F Bronner. New York 1962. Academic Press. 371.
- 17 Nayler W G, editor. Contraction and relaxation in the myocardium. London 1975. Academic Press.
- 18 Davidson S., Passmore R and Brock, J F., editors. Human nutrition and dietetics fifth ed. Edinburgh and London 1972. Churchill Livingstone.
- 19 Caddell J L. Magnesium deficiency in protein-calorie malnutrition. *Ann. N Y Acad Sci* 162 874 1969.
- 20 Seelig M S. Electrographic patterns of magnesium depletion appearing in alcoholic heart disease. *Ann N Y Acad Sci* 162 906 1969.
- 21 McCance R A and Widdowson E M. The composition of foods, M R C Special Report No 297. London 1960. Her Majesty's Stationery Office.

# The effect of chronic cardiac denervation on infarct size following acute coronary occlusion

Carl E Jones Ph D

Michael D Devous Sr, Ph D

John X Thomas Jr Ph D \*

Elise DuPont BS

College Station Texas

The autonomic nervous system exerts considerable influence on the heart and coronary circulation. While this influence is beneficial to the function of the normal heart, during coronary insufficiency, autonomic stimulation may be detrimental to the viability of ischemic myocardium. Thus following acute coronary occlusion, infarct size is reduced by beta adrenergic blockade<sup>1,2</sup> and increased by beta adrenergic stimulation.<sup>3,4</sup> The deleterious effect of beta adrenergic stimulation on ischemic myocardium is generally attributed to the actions on contractile force, heart rate, and secondarily on oxygen demand. However, a full understanding of the mechanisms involved is obscure.<sup>5,6</sup> Alpha adrenergic mechanisms may also be involved in a detrimental effect of autonomic stimulation on the myocardium during coronary insufficiency. The coronary vasculature is under the influence of both an alpha adrenergic constrictor tone and an opposing beta adrenergic dilator tone.<sup>7</sup> Although under normal conditions the beta adrenergic effect on the coronary vasculature predominates, alpha adrenergic activity may increase under certain conditions. For example, alpha adrenergic activity is increased during some forms of coronary insufficiency in humans<sup>8</sup> and there is evidence

that during experimental coronary occlusion alpha adrenergic activity limits collateral flow to ischemic myocardium.<sup>9,10</sup> The coronary vasculature is also innervated by vagal cholinergic fibers which produce vasodilatation,<sup>11</sup> but little is known about the importance of cholinergic influences during coronary insufficiency.

In earlier studies various forms of cardiac denervation have been used to examine the effects of neural influences on the viability of the myocardium following coronary occlusion and the results are contradictory.<sup>12-14</sup> In recent studies using a complete cardiac denervation model we observed dramatic differences between the myocardial response to coronary occlusion in dogs which had undergone denervation 2 weeks prior to the experiment and that in control non-denervated dogs.<sup>1</sup> In non-denervated hearts occlusion of a coronary artery caused contractile force in the muscle supplied by that artery to be reduced by approximately 65 per cent. In denervated hearts contractile force was reduced by only 13 per cent. Furthermore, in non-denervated hearts an intense cyanosis always developed rapidly in the involved muscle. On the contrary, in denervated hearts cyanosis was never observed indicating a substantial collateral flow to the myocardium normally supplied by the occluded vessel. On the basis of these results the present studies were undertaken to examine more closely the effects of chronic cardiac denervation on the myocardial response to acute coronary occlusion.

## Methods

Mongrel dogs of either sex, weighing 14 to 30 kilograms and anesthetized with intravenously administered sodium pentobarbital (30 mg/kg

From the Department of Medical Physiology, Texas A & M University, College of Medicine, College Station, Texas.

This research was supported by National Institutes of Health grant R01 HL20286 and by a grant from the Texas Affiliate of the American Heart Association.

Received for publication Sept 2, 1977.

Accepted for publication Nov 1, 1977.

Reprint requests: Carl E. Jones, Ph.D., Dept. of Medical Physiology, Texas A & M University College of Medicine, Olin E. Teague Research Center, College Station, Texas 77843.

Fellow of Chicago Heart Association Department of Physiology, Loyola University, Stritch School of Medicine, Maywood, Ill.

body weight) were used. Two studies were performed as follows:

**Infarct size study** In these experiments four groups of dogs were used. These consisted of (1) 10 acute controls which were non denervated (2) six acutely denervated dogs in which the heart was denervated immediately prior to coronary occlusion and in which adrenergic blockade was maintained pharmacologically (3) seven chronically denervated dogs in which the heart had been denervated 3 weeks prior to the experiment and (4) four sham operated dogs which 2 weeks prior to the experiment had been subjected to a surgical procedure similar to that involved in chronic cardiac denervation but in which the cardiac nerves had not been cut.

For acute cardiac denervation experiments a femoral artery in each animal was catheterized with a fluid filled Tygon catheter and the catheter tip was positioned in the thoracic aorta. This catheter was connected to a Statham P23AC pressure transducer and the transducer was connected to a Grass model 7D Polygraph for continuous display of arterial pressure (AP). The AP signal was used as the input to a Grass model 7P1F tachograph for display of heart rate (HR). A second Tygon catheter was inserted into a femoral vein for administration of drugs. Each dog was artificially respired with a Harvard model 615 respirator and the chest was entered through the fourth intercostal space on the left side using an electrosurgical unit. The caudal cervical ganglia on each side were stripped and the thoracic vagi as well as the dorsal and ventral ansae were sectioned. Since the myocardial catecholamine level is still high following acute denervation and since there may be intramyocardial adrenergic reflexes not involving extrinsic nerves<sup>10</sup> both an alpha and a beta adrenergic antagonist were administered. To do this a test dose of 0.4 µg/Kg body weight norepinephrine was injected and the HR and AP responses were noted. The beta adrenergic antagonist propranolol (1 mg/kg body weight) and the alpha adrenergic antagonist phentolamine (1mg/kg body weight) were then administered and the responses to a second dose of norepinephrine were obtained. These responses were always abolished immediately after propranolol and phentolamine administration. Coronary occlusion was then performed for the infarct size experiment as described below and at 30 minute intervals test

doses of norepinephrine were repeated. An increase in AP was regarded as evidence of alpha adrenergic stimulation and if this response was seen additional phentolamine (0.3 to 0.5 mg/Kg body weight) was administered. An increase in HR indicated beta adrenergic stimulation and when this was seen additional propranolol (0.3 to 0.5 mg/Kg body weight) was injected.

In each acute control dog a femoral artery was catheterized and HR and AP were monitored as described above. Each animal was artificially respired and the chest was entered through the fourth intercostal space on the left side. After AP and HR stabilized coronary occlusion was performed for the infarct size experiment.

The method used for chronic cardiac denervation has been described previously.<sup>11</sup> Each dog was artificially respired and using sterile techniques the chest was entered through the fourth intercostal space on the left side. The left thoracic vagus nerve (LTV), right thoracic vagus nerve (RTV), left stellate ganglion (LS) and right stellate ganglion (RS) were isolated. The pericardium was opened, a pericardial cradle formed and Walton Brodie strain gauge arches were sutured to the left atrial appendage and to the base of the left ventricle. Recordings of left atrial contractile force (LACF) and left ventricular contractile force (LVCF) were displayed on a Grass polygraph recorder and the output of the LVCF driver amplifier was used as the input to the tachograph for continuous recordings of HR. Following stabilization of all recordings the LTV, RTV, LS and RS were stimulated with a Grass S9 stimulator which delivered square wave pulses of 5 msec duration at a rate of 10/sec and voltages of 4 to 6 v for the vagus nerves and 8 to 10 v for the stellate ganglia. Typical control pre-denervation inotropic and chronotropic responses are illustrated in the top tracings of Fig. 1. After obtaining these responses all cardiac nerves were surgically ablated within the pericardium. The procedure included a careful transection around the complete circumference of the superior vena cava with ligation and division of the azygous vein. The dissection was continued medially from the superior vena cava across the superior surfaces of the right and left atria and pulmonary veins and included section of the ventrolateral cardiac nerve. The adventitia was removed from the complete circumference of the pulmonary artery. All nervous tissue was also removed from



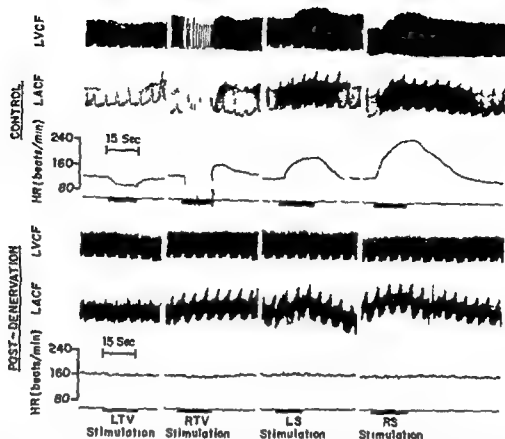


Fig 1 Typical cardiac responses to stimulation of the thoracic vagus nerves and stellate ganglia before (upper tracings) and after (lower tracings) cardiac denervation by the method used in the chronic denervation experiments. HR = heart rate. LACF = left atrial contractile force. LS = left stellate ganglion. LTV = left thoracic vagus nerve. LVCF = left ventricular contractile force. RS = right stellate ganglion. RTV = right thoracic vagus nerve.

between the roots of the pulmonary artery and the ascending aorta. After performing these procedures responses to LTV, RTS, LS and RS stimulation were again obtained in order to ascertain that cardiac denervation was complete. The lower tracings of Fig 1 show the absence of any inotropic or chronotropic response after a complete denervation. When total denervation was assured the strain gauge arches were removed. The pericardium was closed and the chest was closed in layers. Each animal was allowed to recover and was treated with antibiotic (Longicel 1 ml/10 Kg body weight/day) for 4 days. A period of 2 weeks was allowed before experimentation. During this time the myocardial catecholamine level presumably was depleted.<sup>23</sup> Also, our previous studies have suggested a substantial protection against infarction after this time.<sup>24</sup> After 2 weeks each animal was re-anesthetized. AP and HR were monitored as described above and the chest was re-entered through the fourth intercostal space on the left side. Responses to LTV, RTV, LS and RS stim-

ulation were again obtained in order to recheck the completeness of cardiac denervation. Coronary occlusion was then performed for the infarct size experiments as described below.

In the sham operated dogs the chest was opened through the fourth intercostal space using sterile techniques. A pericardial cradle was formed and strain gauge arches were sutured to the left atrial appendage and to the base of the left ventricle. The chest remained open for 3 to 4 hours, at which time the strain gauges were removed and the pericardium and chest were closed. These animals were treated with antibiotic and carefully observed for 2 weeks until the day of the experiment.

The method used to produce a standardized coronary occlusion and to estimate the resulting infarct size was identical in all groups and has been reported previously.<sup>13,25</sup> In each animal a pericardial cradle was formed. Only animals having a normal left anterior descending artery (LAD) distribution were used in the study. Normal LAD distribution was considered to be

present when there were one or more branches of the LAD above the apical branch and when the apical branch originated at approximately the distal end of the middle third of the LAD. If these criteria were satisfied two silk ligatures were placed around the LAD immediately above the apical branch. When AP and HR had stabilized the ligatures were tied. It has been shown that a uniform infarct size can be produced in dogs by occlusion of the LAD in this manner. The LAD occlusion was maintained for a period of 3 hours at which time the animal was killed and the heart was immediately excised. The atrium, the free wall of the right ventricle and all fat were removed from the left ventricle (LV). The LV was then carefully sliced cross sectionally into seven to nine sections approximately 0.7 to 1.0 cm in thickness. The sections were incubated at 37°C in nitro blue tetrazolium (NBT) solution prepared by mixing 250 mg NBT, 80 ml 1M phosphate buffer and 720 ml distilled water. After an incubation period of 10 minutes a clear distinction between infarcted muscle and non-infarcted muscle was apparent. The formazan formed by dehydrogenase activity in the undamaged muscle produced a rich blue color while the infarcted muscle remained unstained. The unstained portion of the LV was carefully cut away from the stained portion and weighed. The weight of the infarct was compared to total LV weight and expressed as a percentage of total LV weight.

**Demonstration of non perfused myocardium**  
In this study two groups of animals were used. These consisted of four dogs in which the heart was chronically denervated as described above and four non-denervated controls which had not been subjected to any prior surgery. In the denervated dogs the stellate ganglia and vagus nerves were re-stimulated on the day of the experiment to re-check the completeness of denervation. Only chronically denervated animals were used since the infarct size studies had already shown that by far the largest effect on infarct size was seen in these animals. Also acute controls rather than sham-operated dogs were used since the previous studies had demonstrated no significant difference between infarct size in acute controls and sham-operated animals.

To demonstrate areas of non perfusion within the myocardium following coronary occlusion

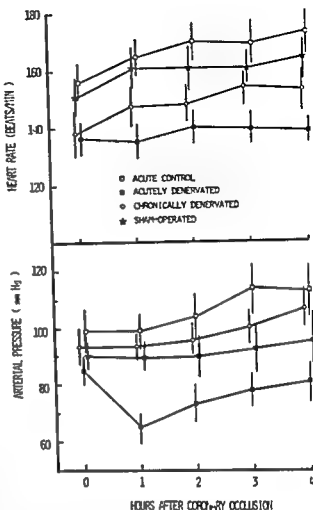


Fig 2 Heart rates and arterial pressures before and following coronary occlusion in the four groups of dogs used in the infarct size study. Vertical bars are standard errors of the mean.

the vital stain thioflavin S was used. This stain binds to endothelium and fluoresces intensely when exposed to ultraviolet light. Thus if a tissue is perfused with thioflavin S is sectioned and exposed to ultraviolet light all areas of tissue which received flow will fluoresce while areas which did not receive flow will appear dark. In these experiments the LAD was ligated above the apical branch as described above. Five minutes after LAD occlusion 1 ml/kg body weight of a 4 per cent solution of thioflavin S was injected through a Tygon catheter inserted into the right atrium via a jugular vein. After a period of 15 seconds the heart was quickly arrested by injection of concentrated KCl and immediately excised. The atria, the free wall of the right

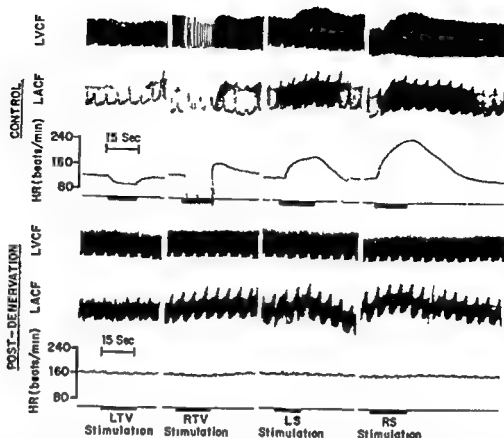


Fig 1 Typical cardiac responses to stimulation of the thoracic vagus nerves and stellate ganglia before (upper tracings) and after (lower tracings) cardiac denervation by the method used in the chronic denervation experiments. HR = heart rate. LACF = left atrial contractile force. LS = left stellate ganglion. LTV = left thoracic vagus nerve. LVCF = left ventricular contractile force. RS = right stellate ganglion. RTV = right thoracic vagus nerve.

between the roots of the pulmonary artery and the ascending aorta. After performing these procedures, responses to LTV, RTS, LS and RS stimulation were again obtained in order to ascertain that cardiac denervation was complete. The lower tracings of Fig 1 show the absence of any inotropic or chronotropic response after a complete denervation. When total denervation was assured, the strain gauge arches were removed. The pericardium was closed, and the chest was closed in layers. Each animal was allowed to recover and was treated with antibiotic (Longicil 1 ml/10 Kg body weight/day) for 4 days. A period of 2 weeks was allowed before experimentation. During this time the myocardial catecholamine level presumably was depleted.<sup>13,14</sup> Also, our previous studies have suggested a substantial protection against infarction after this time.<sup>1</sup> After 2 weeks, each animal was re-anesthetized. AP and HR were monitored as described above, and the chest was re-entered through the fourth intercostal space on the left side. Responses to LTV, RTV, LS and RS stim-

ulation were again obtained in order to re-check the completeness of cardiac denervation. Coronary occlusion was then performed for the infarct size experiments as described below.

In the sham-operated dogs, the chest was opened through the fourth intercostal space using sterile techniques. A pericardial cradle was formed, and strain gauge arches were sutured to the left atrial appendage and to the base of the left ventricle. The chest remained open for 3 to 4 hours at which time the strain gauges were removed and the pericardium and chest were closed. These animals were treated with antibiotic and carefully observed for 2 weeks until the day of the experiment.

The method used to produce a standardized coronary occlusion and to estimate the resulting infarct size was identical in all groups and has been reported previously.<sup>12,15</sup> In each animal, a pericardial cradle was formed. Only animals having a normal left anterior descending artery (LAD) distribution were used in the study. Normal LAD distribution was considered to be

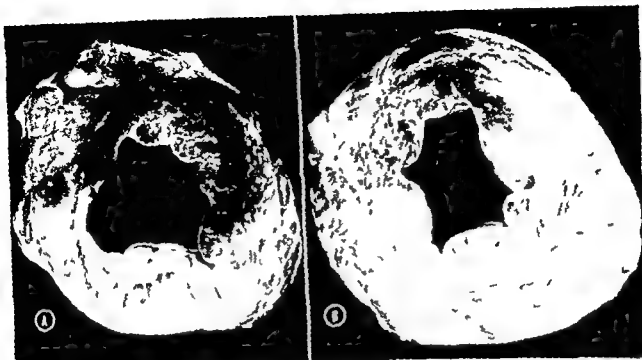


Fig 3 A and B A section of left ventricle obtained from an acute control (A) and a chronically denervated (B) heart comparing the quantity of non perfused myocardium produced by acute coronary occlusion. The dark areas are the regions of muscle which were non perfused.

the chronically denervated animals mean infarct size in this group was only 3.8 per cent of LV weight. It is remarkable that two of the hearts in the chronically denervated group had infarct sizes of less than 1 per cent and five hearts had infarct sizes of less than 4 per cent. This large reduction in infarct size following chronic denervation was apparently not due to a promotion of coronary collateral growth caused by the opening of the pericardium and the ensuing irritation of the epicardial surface since the mean infarct size in the sham operated group was not statistically different from that seen in the acute controls.

#### Determination of non perfused myocardium

Figs 3A and 3B show typical results obtained from an acute control heart (A) and from a chronically denervated heart (B). The light areas in the heart sections are those areas of the myocardium which were perfused prior to arrest and excision of the heart. The dark areas are those portions of myocardium which were not perfused. From these photographs it is evident that the quantity of muscle which was non perfused is much smaller in the chronically denervated heart than in the acute control heart. The results shown in Fig 3 are exemplary of all

animals used in this study with the exception of one dog in the chronically denervated group which showed a slight inotropic response to RS stimulation when the completeness of cardiac denervation was checked on the day of the experiment. In this case IVCF was increased 110 per cent when the RS was stimulated prior to the denervation procedure and 20 per cent when the RS was stimulated 2 weeks after the procedure. This animal was the only one of the chronically denervated group which showed a residual response to either vagal or stellate stimulation and it is interesting that the size of the non perfused myocardium in this heart was similar to that commonly observed in acute control hearts.

#### Discussion

The results presented in this paper clearly demonstrate that both chronic cardiac denervation and acute denervation with adrenergic blockade result in a substantially reduced infarct size following acute coronary occlusion. These results also demonstrate that the protective effect of cardiac denervation is enhanced with time such that the infarct produced by coronary occlusion

**Table 1** Analysis of infarct sizes in acute control acutely denervated, chronically denervated, and sham operated hearts

| Dog no                               | Infarct weight (Gm) | Left ventricular weight (Gm) | % infarct |
|--------------------------------------|---------------------|------------------------------|-----------|
| <i>Acute controls</i>                |                     |                              |           |
| 10                                   | 10.7                | 53.6                         | 20.0      |
| 11                                   | 17.3                | 97.6                         | 17.7      |
| 12                                   | 18.1                | 87.8                         | 20.6      |
| 13                                   | 10.0                | 46.5                         | 21.5      |
| 15                                   | 17.0                | 99.0                         | 17.3      |
| 16                                   | 14.2                | 71.6                         | 19.8      |
| 20                                   | 12.9                | 75.8                         | 17.0      |
| 24                                   | 20.0                | 80.7                         | 24.8      |
| 29                                   | 13.1                | 66.3                         | 19.8      |
| 40                                   | 27.9                | 126.7                        | 22.0      |
| MEAN                                 | 16.1                | 80.5                         | 20.1      |
| SE                                   | 1.7                 | 7.4                          | 0.80      |
| <i>Acutely denervated hearts</i>     |                     |                              |           |
| 36                                   | 18.1                | 101.1                        | 17.9      |
| 37                                   | 18.1                | 103.0                        | 17.6      |
| 38                                   | 11.7                | 93.7                         | 12.5      |
| 42                                   | 9.2                 | 81.2                         | 11.4      |
| 43                                   | 12.5                | 67.2                         | 18.6      |
| 45                                   | 12.2                | 100.4                        | 12.1      |
| MEAN                                 | 13.7                | 91.1                         | 15.0      |
| SE                                   | 1.5                 | 5.8                          | 1.4       |
| P                                    | —                   | —                            | 0.004     |
| <i>Chronically denervated hearts</i> |                     |                              |           |
| 14                                   | 5.5                 | 72.4                         | 7.7       |
| 17                                   | 3.0                 | 97.0                         | 3.1       |
| 19                                   | 0.5                 | 82.7                         | 0.6       |
| 22                                   | 8.9                 | 92.4                         | 9.7       |
| 25                                   | 0.7                 | 87.0                         | 0.8       |
| 28                                   | 1.1                 | 91.7                         | 1.2       |
| 33                                   | 1.7                 | 50.8                         | 3.9       |
| MEAN                                 | 3.1                 | 82.0                         | 3.8       |
| SE                                   | 1.2                 | 6.0                          | 1.4       |
| P                                    | —                   | —                            | <0.001    |
| <i>Sham Operated hearts</i>          |                     |                              |           |
| 26                                   | 19.9                | 97.4                         | 20.5      |
| 30                                   | 24.9                | 93.6                         | 26.6      |
| 32                                   | 19.5                | 87.4                         | 22.3      |
| 35                                   | 18.0                | 123.0                        | 14.7      |
| MEAN                                 | 20.6                | 100.4                        | 21.0      |
| SE                                   | 1.5                 | 7.8                          | 2.5       |
| P                                    | —                   | —                            | 0.633     |

ventricle and all fat were trimmed from the LV and the LV was sectioned as in the infarct size experiments. The LV sections were then photographed under ultraviolet light (360 mμ) using a Tyssen No 12 barrier filter Kloner and co workers<sup>11</sup> used thioflavin S to delineate non perfused myocardium after coronary occlusion

and quantitated the area of non perfusion by planimetry of the photographic image. However we observed that the non perfused muscle was often very nonuniform in distribution such that planimetry was difficult and imprecise. Nevertheless large differences in the quantity of non perfused muscle between the non denervated and denervated hearts could be qualitatively discerned by visual examination.

## Results

**Infarct size study** Fig 2 shows the changes in mean HR and AP following coronary occlusion in the four groups of animals used in this study. Changes in HR and AP are illustrated only for the first 4 hours following coronary occlusion. It is felt that only during this period were these hemodynamic parameters important in influencing infarct size. HR in the sham operated dogs was not significantly different from that in the acute controls at the time of coronary occlusion, and it did not differ from that in the acute controls at any time following coronary occlusion ( $P > 0.05$ ). HR in both the chronically denervated and acutely denervated animals was significantly less than that in the acute controls at the time of coronary ligation, and both remained significantly less at all times ( $P < 0.05$ ). AP in the chronically denervated and the sham operated dogs was not significantly different from that in acute controls either at the time of ligation or at any time during the 4 hour period of observation. However AP in the acutely denervated animals was significantly less than that in acute controls at the time of ligation and at all intervals following ligation.

Table I illustrates an analysis of infarct sizes found in the hearts of these animals. In this table P values for infarct sizes in the acutely denervated, chronically denervated and sham operated groups represent significance when compared to acute controls. Note in Table I that within the acute control animals observed infarct sizes were very consistent and this small dispersion indicates the reproducibility of the method used for infarct size determination. Mean infarct size in the acutely denervated dogs was 15.0 per cent of LV weight compared 20.1 per cent in the acute controls. The difference was statistically significant. However it can be seen that a far greater reduction in infarct size was observed in

a 2 week period.<sup>20</sup> However the precise factors which initiate a growth of collaterals are not sufficiently defined to predict their role in the completely denervated heart.

# Summary

The effect of acute coronary ligation on infarct size was studied in (1) ten acute control dogs which were non denervated (2) in six acutely denervated dogs in which the heart was denervated immediately prior to coronary ligation and in which intra-cardiac reflexes were pharmacologically blocked (3) in seven chronically denervated dogs in which intrapericardial nerves were cut 2 weeks prior to ligation and (4) in four dogs which were sham operated 2 weeks prior to ligation. Infarct size was determined using a nitro blue tetrazolium stain for dehydrogenase activity. Infarct sizes in acute controls acutely denervated chronically denervated and sham operated hearts were 20.1, 15.0, 3.6 and 21.0 per cent of left ventricular weight respectively. Infarct sizes in acutely and chronically denervated hearts were significantly less than in acute controls ( $P < 0.05$ ). In further studies the fluorescent stain thioflavin S was used to demonstrate that perfusion of myocardium distal to the ligation was substantially greater in chronically denervated hearts than in acute controls.

The authors wish to thank Miss Teresa Stoddard for typing the manuscript, Mr Timothy Manning for his photographic assistance and Dr Walter C Randall for his graciousness in teaching us the method used for chronic denervation of the heart.

# REFERENCES

- Pierce W S, Carter D R, McGavran M H and Waldhausen J A. Modification of myocardial infarct volume. *Arch. Surg.* 107: 682, 1953.
- Reuser K A, Rasmussen M and Jennings R B. Reduction by propranolol of myocardial necrosis following temporary coronary occlusion in dogs. *Circ. Res.* 33: 353, 1973.
- Reuser K A, Rasmussen M M and Jennings R B. On the nature of protection by propranolol against myocardial necrosis after temporary coronary occlusion in dogs. *Am. J. Cardiol.* 37: 520, 1976.
- Moroko P R, Kyekahus J K, Sobel B E, Watanabe T, Covell J W, Ross J Jr and Braunwald E. Factors influencing infarct size following experimental coronary artery occlusion. *Circulation* 43: 67, 1971.
- Moroko P R, Libby P, Covell J W, Sobel B E, Ross J Jr and Braunwald E. Precordial S-T segment elevation mapping: an atraumatic method for assessing alteration in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. *Am. J. Cardiol.* 29: 223, 1972.

- Lesch M. Inotropic agents and infarct size: theoretical and practical considerations. *Am. J. Cardiol.* 37: 508, 1976.
- Laang C and Hood W B Jr. The myocardial depressant effect of beta receptor blocking agents: comparative study of di propranolol, d propranolol and practolol in awake dogs with and without acute myocardial infarction. *Circ. Res.* 35: 772, 1974.
- Becker L C, Ferreira R, and Thomas M. Effect of propranolol and isoprenaline on regional left ventricular blood flow in experimental myocardial ischemia. *Cardiovasc. Res.* 9: 178, 1975.
- Pace J B. Autonomic control of the coronary circulation. chapter 11 in *Neural Regulation of the heart*. Randall W C ed. New York 1977. Oxford University Press, p. 377.
- Mudge G H, Jr, Crossman W, Milla, R M, Jr, Lesch M and Braunwald E. Reflex increase in coronary vascular resistance in patients with ischemic heart disease. *N. Engl. J. Med.* 295: 1333, 1976.
- Grayson J, Irvine M, Paratt J R and Cunningham J. Vasoactive elements in myocardial infarction following coronary occlusion in the dog. *Cardiovasc. Res.* 2: 54, 1969.
- Feigl E O. Parasympathetic control of coronary blood flow in dogs. *Circ. Res.* 25: 509, 1969.
- Lenche R and Fontaine R. Les résultats actuels du traitement chirurgical de l'angine de poitrine. *J. Chir.* 38: 785, 1931.
- Lenche R, Herrmann L and Fontaine R. Ligature de la coronarie gauche et fonction cardiaque chez l'animal intact. *Compt. Rend. Soc. Biol.* 107: 545, 1931.
- Cox W B and Robertson H P. The effect of stellate ganglionectomy on the cardiac function of intact dogs and its effect on the extent of myocardial infarction and on cardiac function following coronary artery occlusion. *Am. Heart J.* 12: 285, 1936.
- Fautoux M. Surgical treatment of angina pectoris: experiences with ligation of the great cardiac vein and pericoronary neurectomy. *Ann. Surg.* 124: 1041, 1946.
- Schauer G, Gross, L. and Blum L. Hemodynamic studies in experimental coronary occlusion. *Am. Heart J.* 14: 669, 1937.
- Yodanis C. Sympathectomy and experimental occlusion of a coronary artery. *Am. Heart J.* 22: 545, 1941.
- Thomas J X Jr, Randall W C, Jones C E and Rozenski, D. Effect of coronary occlusion on contractile force in the denervated heart (Abstr). *Fed. Proc.* 36: 1316, 1977.
- Randall W C and Armour J A. Gross and microscopic anatomy of the cardiac innervation. chapter 2 in *Neural regulation of the heart*. Randall W C ed. New York 1977. Oxford University Press, p. 30.
- Randall W C, Kaye M, Hageman G R, Jacobs H K, Euler D E and Wehrmacher W. Cardiac dysrhythmias in the conscious dog after surgically induced autonomic imbalance. *Am. J. Cardiol.* 38: 179, 1976.
- Kaye M P. Denervation and reinnervation of the heart. chapter 12 in *Neural regulation of the heart*. Randall W C ed. New York 1977. Oxford University Press, p. 351.
- Cooper T, Willman V L, Jelinek M and Hanlon C R. Heart autotransplantation: effect on myocardial catecholamines and histamine. *Science* 138: 40, 1972.
- Greg D E, Khoun E M, Donald D E, Lowensohn H S and Pasik S. Coronary circulation in the conscious dog with cardiac neural ablation. *Circ. Res.* 31: 129, 1972.

in the chronically denervated heart is much smaller than that produced in the acutely denervated heart. Possible mechanisms involved in these effects are discussed below.

**Acute cardiac denervation with adrenergic blockade** Since selective parasympathectomy or sympathectomy were not performed in the present experiments, it is impossible to state with certainty whether the reduction in infarct size was due to removal of parasympathetic or sympathetic influences. However, because certain earlier studies have indicated that selective sympathectomy results in a reduction in infarct size following acute coronary occlusion<sup>12,13</sup> because more recent studies have suggested a beneficial effect of beta adrenergic blockade,<sup>14,15</sup> and because of evidence indicating that alpha adrenergic constrictor activity may be increased during coronary insufficiency<sup>10,11</sup> it is felt that the effects observed were due primarily to removal of sympathetic influences.

The reduction in infarct size observed with acute cardiac denervation and adrenergic blockade is quantitatively similar to that observed following beta adrenergic blockade alone when infarct size was determined by the NBT method used here.<sup>16</sup> Beta adrenergic blockade is thought to exert its effect by reducing heart rate, and consequently increasing diastolic myocardial perfusion and by decreasing myocardial oxygen demand.<sup>8</sup> In the present experiments heart rate in the acutely denervated animals was substantially less than that in acute controls. However the systemic perfusion pressure in the acutely denervated animals was also less than that in acute controls, and it is difficult to assess the net effect of the reduced heart rate and the reduced perfusion pressure. Nevertheless it is probable that the reduction in infarct size observed following acute cardiac denervation with adrenergic blockade has largely the same basis as that observed following beta adrenergic blockade alone.

**Chronic cardiac denervation** The mechanisms responsible for the dramatic reduction in infarct size seen in the chronically denervated heart are entirely unknown. However, it is apparent that these mechanisms are much more effective than those operative in the acute experiments.

The metabolism of the chronically denervated heart is not well defined but Gregg and asso-

ciates<sup>4</sup> have reported that oxygen consumption of the chronically denervated heart is approximately 50 per cent of that in the non denervated heart. The denervation technique used by Gregg and colleagues was different from that used in this study, and oxygen consumption was not measured in the present experiments. But if the finding of Gregg and colleagues can be applied to the chronically denervated animals seen in this study, such a reduced oxygen demand would be expected to maintain viability of myocardium especially in the borderline regions.

In addition to the possible effects of a reduced oxygen demand, it is apparent from the thioflavin S studies that in the chronically denervated heart there was a substantially improved perfusion of the myocardium distal to the coronary ligation. It has been suggested that mechanical irritation of the epicardial surface promotes an increased vascularity of the epicardium.<sup>17</sup> However the results obtained in sham operated dogs demonstrate that this effect cannot explain the improved perfusion seen in the chronically denervated hearts. The sham operated animals were subjected to the same epicardial irritation as the chronically denervated animals, but showed no reduction in infarct size following acute coronary occlusion. It appears more likely that the improved collateral perfusion and the reduction in infarct size were due to some chronic effect of sympathectomy. The results obtained from the one incompletely denervated animal in the chronically denervated group add credence to this proposal. Thus this animal showed no cardiac response to vagal stimulation, no response to left stellate ganglion stimulation and only a slight response to right stellate ganglion stimulation. But this animal showed a greater quantity of non perfused myocardium than any other animal in the chronically denervated group.

Whether the increased perfusion of myocardium distal to the ligation was due to a removal of constrictor activity from existing collaterals or to a growth of additional collaterals is uncertain. The apparently substantial reduction in non perfused myocardium in conjunction with the difference in infarct size between chronically denervated and acutely denervated hearts with adrenergic blockade may indicate an actual growth of new channels. It is known that a substantial growth of collaterals can occur within

# The significance of hypotension developing during treadmill exercise testing\*

Rafael Levites MD FACC\*\*  
 Thomas Baker MD\*\*\*  
 Gary J Anderson MD FACC \*\*\*  
 Philadelphia Pa

Graded treadmill exercise testing is a useful non invasive method of determining not only the presence of significant coronary artery disease but also of assessing the functional capacity of the patient. In addition to the development of horizontal depression of the ST segment various other parameters such as the blood pressure response, arrhythmias, and chest pain can be useful in the overall evaluation of an exercise test. A rise in systolic blood pressure during exercise testing is the normal response. On the other hand a fall in systolic pressure during exercise has been suggested as a reliable sign of marked left ventricular dysfunction secondary to critical coronary artery disease.

This study was undertaken to evaluate the significance of exercise induced hypotension and to better define the relationship of the hypotensive response to the findings at cardiac catheterization. In order to determine the underlying pathology present in patients developing hypotension during exercise testing we have evaluated the coronary anatomy and resting left ventricular function of a group of patients with this sign. In

addition to clarify further those angiographic and hemodynamic findings associated with hypotension we have compared these observations to a group of patients with normal blood pressure response to exercise.

## Methods

The study group was composed of patients evaluated for chest pain and referred for treadmill testing. Exercise tests were performed in the fasting state and medications were discontinued for at least 3 days before testing. Nitroglycerin was withheld the day of treadmill testing. Patients were exercised by the protocol of Bruce employing a modified bipolar V<sub>1</sub> chest lead. Exercise was continued until 90 per cent or more of the predicted maximal heart rate was achieved. Ischemic changes appeared and/or hypotension or angina developed. Cuff blood pressure was measured over the brachial artery employing a sphygmomanometer and recorded standing at rest during the final minute of each 3 minute stage and at the onset of angina, dizziness or ST segment depression. Hypotension during exercise testing was defined as a fall in systolic pressure below the resting level. If hypotension was confirmed by a second measurement made within 20 seconds the test was stopped. An ischemic response was defined as horizontal or down sloping ST segment depression of at least 1 mm (10) of 0.08 sec duration or greater.

Over a two year period from July 1974 to June 1976 1105 patients underwent treadmill testing for suspected coronary artery disease. Thirty patients exhibited hypotension during the exercise test comprising 2.7 per cent of the total

From the William Lukoff Cardiovascular Institute of the Hahnemann Medical College Philadelphia Pa.  
 Received for publication April 6, 1977.  
 Accepted for publication August 4, 1977.  
 Reprint requests: Rafael Levites MD, Cardiology Division, St. Francis Medical Center, 601 Hamilton Avenue, Trenton, NJ 08629.  
 Present address: Dr. Levites, 49th Street, Suite 505, The American Heart Association, Miami, FL, November 1976.  
 Assistant Director of Heart Station, William Lukoff Cardiovascular Institute.  
 Fellow in Cardiology, William Lukoff Cardiovascular Institute.  
 Director of Heart Station, William Lukoff Cardiovascular Institute.



- 25 Nachlas M M and Shnitka T K Macroscopic identification of early myocardial infarct by alterations in dehydrogenase activity *Am J Pathol* 42 379 1963
- 26 Shatney C H MacCarter D J and Lillehei H C Effects of allopurinol propranolol and methylprednisolone on infarct size in experimental myocardial infarction *Am J Cardiol* 37 572 1976
- 27 Kloner R A Ganote C E and Jennings H B The no reflow phenomenon after temporary coronary occlusion in the dog *J Clin Invest* 54 1496 1974
- 28 Kloner R A Ganote C E Reimer K A and Jennings R B Distribution of coronary arterial flow in acute myocardial ischemia *Arch Pathol* 99 86 1975
- 29 Gregg D E Coronary collateral circulation symposium Introduction to the problem *Acta Cardiol (Brux) Suppl* 13 1 1969
- 30 Gregg D E The natural history of coronary collateral development *Circ Res* 35 335 1974

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published. The author(s) warrants that the article is original is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

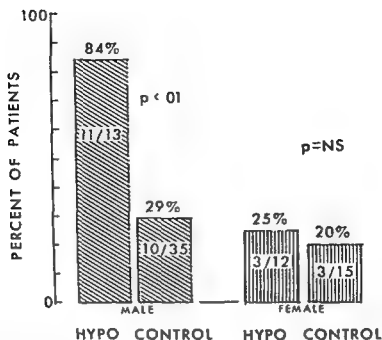


Fig 1 The number of positive exercise tests was significantly higher in hypotensive males compared to control males (84 per cent and 29 per cent). Females had a similar number of positive exercise tests (25 per cent and 20 per cent). *Hypo* = hypotensive group

A positive exercise test was observed in four of the 25 patients in Group I (56 per cent) compared to 13 of the 50 patients in Group II (26%) ( $p < 0.02$ ). When males and females were considered separately it was noted that males accounted for most of the positive exercise tests in both groups: 11 of 14 (76 per cent) in Group I and 10 of the 13 (77 per cent) in Group II (Table II). Furthermore the incidence of positive exercise tests was significantly higher in Group I males (11 of 13 tests: 84 per cent) when compared to females in the same group (three of 12 tests: 25 per cent) or when compared to Group II males (10 of 35 tests: 29 per cent) (both  $p < 0.01$ ) (Fig 1). Females in both groups had a similar incidence of positive exercise tests: 25 per cent in Group I and 20 per cent in Group II (Fig 1).

**Hemodynamic and angiographic correlates**  
The findings at cardiac catheterization are tabulated in Table III. Mean left ventricular end diastolic pressures were similar (12.2 vs 11.6 mm Hg) although the control group had a slightly higher frequency of patients with left ventricular end diastolic pressures over 14 mm Hg (26 per cent vs 20 per cent). The mean cardiac index and the percentage of patients with a cardiac index

below 2.5 L/min/M<sup>2</sup> was not different in both groups of patients.

Although the incidence of coronary artery disease in Group I was 52 per cent (13 of 25 patients) compared to 36 per cent (18 of 50 patients) in the control group this difference was not statistically significant ( $p = NS$ ). As mentioned above the incidence of positive exercise tests in Group I was 56 per cent of which one was a false positive test. In Group II there were three submaximal and two false negative tests. Therefore the difference in positive exercise tests between Groups I and II (56 per cent vs 26 per cent) is due to the higher frequency of inadequate and false negative tests in the control group and the presence of one false positive test in the hypotensive group.

When males and females were considered separately it was noted that the majority of patients with coronary artery disease were males: 10 of 13 patients in Group I and 14 of 18 patients in Group II both 77 per cent. It was also apparent that the incidence of significant coronary artery disease was higher among hypotensive males: 10 of 13 (77 per cent) when compared to control males: 14 of 35 (40 per cent) ( $p < 0.01$ ) (Fig 2). Females had a

Table I Clinical characteristics

|                       | Group I<br>(25 patients) |       | Group II<br>(50 patients) |       |
|-----------------------|--------------------------|-------|---------------------------|-------|
|                       | Range                    | Mean  | Range                     | Mean  |
| Sex                   |                          |       |                           |       |
| Male                  | 13 (52%)                 |       | 35 (70%)                  |       |
| Female                | 12 (48%)                 |       | 15 (30%)                  |       |
| Age (yrs)             | 37-62                    | 50.2  | 25-69                     | 46.8  |
| Resting BP<br>(mm Hg) |                          |       |                           |       |
| Systolic              | 106-170                  | 124.8 | 94-200                    | 123.7 |
| Diastolic             | 70-100                   | 78.5  | 60-105                    | 77.9  |
| Previous MI           | 6 (24%)                  |       | 8 (16%)                   |       |

BP = blood pressure MI = myocardial infarction yrs = years

Table II Results of treadmill exercise test

|                                | Group I<br>(25 patients) |       | Group II<br>(50 patients) |       |
|--------------------------------|--------------------------|-------|---------------------------|-------|
|                                | Range                    | Mean  | Range                     | Mean  |
| Duration (sec)                 | 130-840                  | 420.2 | 30-840                    | 487.3 |
| FAI (%)                        | (-20)-<br>(+58)          | +13.1 | (-20)-<br>(+75)           | +8.4  |
| Max HR                         | 117-175                  | 146.5 | 90-185                    | 152.5 |
| Change in HR                   | 22-111                   | 59.8  | 32-89                     | 69.2  |
| Fall in systolic<br>BP (mm Hg) |                          |       |                           |       |
| From control                   | 8-60                     | 21    | -                         | -     |
| From peak                      | 20-110                   | 34.8  | -                         | -     |
| ST depression<br>(mm)          | 1-5                      |       | 1-4                       |       |
| Positive test                  | 14 (11<br>males)         |       | 13 (10<br>males)          |       |

FAI = functional aerobic impairment HR = heart rate BP = blood pressure Max = maximal

Table III Cardiac catheterization findings

|                            | Group I<br>(25 patients) |      | Group II<br>(50 patients) |      |
|----------------------------|--------------------------|------|---------------------------|------|
|                            | Range                    | Mean | Range                     | Mean |
| LVEDP (mm Hg)              | 3-35                     | 12.2 | 2-24                      | 11.6 |
| LVEDP > 14                 | 5 (20%)                  |      | 13 (26%)                  |      |
| CI (l/min/m <sup>2</sup> ) | 1.32-4.80                | 2.8  | 1.84-4.43                 | 2.92 |
| CI < 2.5                   | 7 (28%)                  |      | 12 (24%)                  |      |
| CAD patients               | 13 (10 males)            |      | 18 (14 males)             |      |
| Vessels involved           |                          |      |                           |      |
| 1                          | 4                        |      | 8                         |      |
| 2                          | 4                        |      | 5                         |      |
| 3                          | 4                        |      | 5                         |      |
| LM                         | 1                        |      | -                         |      |

LVEDP = left ventricular end-diastolic pressure CI = cardiac index  
CAD = coronary artery disease LM = left main coronary artery

number of patients exercised. Five of these patients refused further evaluation and were excluded from the study. In the remaining 25 patients, cardiac catheterization was performed within 2 weeks of the exercise test. These 25 patients (Group I) were compared to a group of 50 consecutive unselected patients that underwent exercise testing and had a normal blood pressure response (Group II). Coronary arteriography by the Judkins<sup>11</sup> or Sones and Shirey<sup>12</sup> techniques was performed in all patients in multiple projections using Renograffin 76 per cent. Significant coronary artery disease was defined as obstruction  $\geq 75$  per cent in one or more of the major vessels.

Statistical significance was determined using the chi square and Student's *t* test for nonpaired data.

## Results

**Clinical characteristics** There were 25 patients in Group I and 50 patients in the control group. In Group I there were 13 males (52 per cent) and 12 females (48 per cent) compared to 35 males (70 per cent) and only 15 females (30 per cent) in the control group (*P* = NS) (Table I). The mean age was comparable: 50.2 years in Group I and 46.8 years in Group II. Mean resting blood pressure was similar in both groups. A history of previous myocardial infarction was comparable in Groups I and II (24 per cent vs 16 per cent).

**Treadmill testing correlations** Table II summarizes the results of exercise testing. Patients with hypotension manifested a decrease in mean exercise duration (420 sec vs 487 sec) and their mean aerobic capacity was slightly lower (+13.1 per cent vs +8.4 per cent) when compared to the control patients, but these differences were not statistically significant. The mean maximal heart rate and the mean change in rate (from control to maximal) were also similar in both groups of patients. However, only two Group I patients (8 per cent) achieved 90 per cent of their predicted target rate compared to 19 Group II patients (38 per cent) (*p* < 0.01). In those patients developing hypotension, the mean fall in systolic blood pressure was 21 mm Hg from resting levels and 34.8 mm Hg from peak pressure achieved during the exercise performance. By definition, no drop in blood pressure was seen among the patients in the control group.

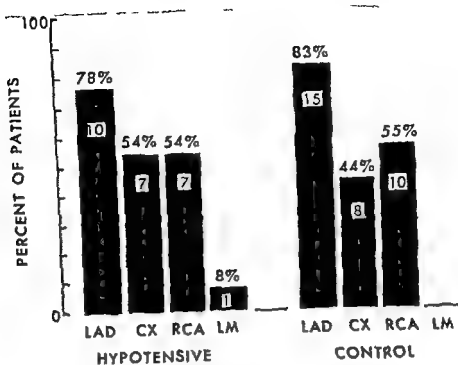


Fig 3 The distribution of vessels with significant obstruction was similar in hypotensive and control groups. The vessel most frequently involved was the left anterior descending coronary artery

portion of the left ventricular mass became ischemic thus producing left ventricular dysfunction. However it is difficult to ascertain the severity of coronary artery disease in hypotensive patients unless a group of patients with normal blood pressure response is available for comparison.

Although in this study no attempt was made to identify the immediate physiologic mechanisms that led to hypotension, we believe it is important to better define the pathologic findings present in hypotensive patients which may contribute to the development of this abnormal response.

Clinical characteristics were similar in both groups of patients but it was interesting to note the higher percentage of females in the hypotensive group (Table I). However (nine of 12) 75 per cent of the female patients in this group had normal coronary arteries, an incidence similar to the one observed in control females. Based on the angiographic findings (see Results section) five of these nine hypotensive patients were considered normal, two had mitral valve prolapse without mitral regurgitation and two had findings compatible with a cardiomyopathy. All had normal or in one case borderline left ventricular

end-diastolic pressures. These findings suggest that a hypotensive response in females might not connote coronary artery disease nor severe left ventricular dysfunction. This result is in agreement with the findings of Thomson and Keleman who in their study of 15 patients with coronary artery disease and exercise induced hypotension found only one female.

Although the incidence of positive treadmill tests was significantly higher in the hypotensive group, the incidence of coronary disease was not different between groups as a whole. This apparent discrepancy is clarified if one realizes that there were three submaximal and two false negative tests in the control group and one false positive test in the hypotensive group. Of interest was the fact that when males and females were considered separately, the incidence of coronary artery disease was higher among males with hypotension compared to control males (77 per cent vs 40 per cent  $p < 0.01$ ). However the results of this study showed no correlation between exercise induced hypotension and the absence or presence of coronary artery disease. Moreover the number and distribution of diseased vessels and the severity of involvement

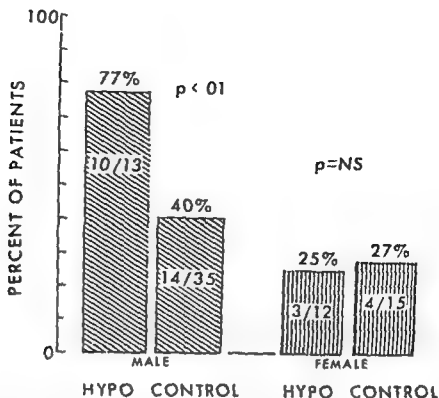


Fig 2 The number of patients with significant coronary artery disease was higher in hypotensive males compared to control males (77 per cent and 40 per cent). Females had a lower but comparable incidence of coronary artery disease (25 per cent and 27 per cent). Hypo = hypotensive group.

similar incidence of significant coronary disease, 25 per cent in Group I and 27 per cent in Group II (Fig 2). However, no significant differences were noted in the degree of narrowing or number of diseased vessels between groups (Table III). Males accounted for the majority of patients with two vessel disease and for all patients with three vessel disease in both groups. In addition, the distribution of coronary lesions showed predominant involvement of the left anterior descending coronary artery in both groups: 78 per cent and 83 per cent in Groups I and II respectively, and a similar distribution of left circumflex and right coronary artery narrowing. An isolated narrowing of the left main coronary artery was seen in one patient with hypotension (Fig 3).

Nine of the 12 females in Group I (75 per cent) did not have significant coronary artery disease. Five of the nine had normal left ventricular end diastolic pressures and normal left ventriculograms. Two had normal left ventricular end diastolic pressures, abnormal ventriculograms and mitral valve prolapse without mitral regurgitation. Two had abnormal ventriculograms: one with a left ventricular end diastolic pressure and 15 mm Hg and the other with normal pressures.

Three of the 13 males in Group I (23 per cent) were free of significant coronary artery disease. All three had normal left ventricular end diastolic pressures: two with abnormal and one with normal left ventriculograms.

### Discussion

The role of exercise testing as a non invasive diagnostic tool in patients with suspected coronary artery disease is well established. Constant monitoring of physiologic parameters during the exercise performance is important not only for reasons of safety, but for the opportunity to detect abnormal responses. One such abnormal response to exercise is a drop in systolic blood pressure. However, the significance of exercise induced hypotension in patients evaluated for chest pain and its value as a predictor of coronary artery disease remains to be determined.

Exercise induced hypotension has been reported as a reliable sign of severe coronary artery disease.<sup>1</sup> Thomson and Kelemen<sup>2</sup> described 15 patients with hypotension accompanying the onset of angina and postulated that critical coronary artery narrowing caused the systolic pressure to fall because during exercise a large

- Andrus, W. and Fuller T. Exertional hypotension in cardiac patients. *Circulation* 19 543 1959
4. Thomson, P., and Kelemen M. Hypotension accompanying the onset of exertional angina. *Circulation* 52 28 1955
  5. Gooch, A. Exercise testing for detecting changes in cardiac rhythm and conduction. *Am J Cardiol* 30 741 1972
  6. Anderson M, Lee H, Campion B, Amplatz, K. and Tuna N. Cardiac dysrhythmias associated with exercise stress testing. *Am J Cardiol* 30 763 1972
  7. Rushmer H F. *Cardiovascular Dynamics*. Philadelphia W.B. Saunders 1961 p 180
  8. Bruce R.A., Gey G O, Cooper M N, Fisher L D., and Peterson D R. Seattle Heart Watch: Initial clinical circulatory and electrocardiographic responses to maximal exercise. *Am J Cardiol* 33 459 1974
  9. Bruce R A. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res* 3 323 1971
  10. Mattus, A. Exercise electrocardiography. Recognition of the ischemic response. False positive and negative patterns. *Am J Cardiol* 33 721 1974
  11. Judkins, M P. Percutaneous transfemoral selective coronary arteriography. *Radiol. Clin North Am.* 6 467 1968
  12. Sones F M. and Shurey E K. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis.* 31 73 1962
  13. Bruce R A. Methods of exercise testing. Step test, bicycle treadmill, isometrics. *Am. J Cardiol* 33 15 1974

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore all manuscripts must be accompanied by the following statement signed by each author. The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C. V. Mosby Company in the event the work is published. The author(s) warrants that the article is original, is not under consideration by another journal, and has not been previously published. Authors will be consulted when possible regarding republication of their material.

did not differ between groups. Equally striking was the similarity in the resting mean end diastolic pressure and cardiac index between groups and the comparable number of patients with wall motion abnormalities.

The hypotensive response to exercise may not imply left ventricular dysfunction potentially secondary to ischemia. Hypotension can occur in normal subjects during maximal exhaustive exercise. This is accepted as a normal event since it occurs when subjects enter an anaerobic phase of exercise. However, only two of the patients in the hypotensive group reached 90 per cent of their predicted maximal heart rate and these rates were attained at low levels of exercise. Since heart rate and anaerobic metabolism do not appear to be the determinants in the hypotensive responses that were observed, other variables must be playing a role. Vasovagal responses can be responsible for exercise induced hypotension, but in this case hypotension occurs in the post exercise period and is associated with bradycardia. None of our patients demonstrated this type of response. The major determinants of blood pressure during exercise include heart rate, myocardial contractility and the response of the peripheral vascular system, especially to circulating catecholamines.<sup>1</sup> A primary impairment of the autonomic system appears unlikely, since none of our patients developed orthostatic hypotension. The pressure changes during exercise are an index of the inotropic reserve of the left ventricle.<sup>12</sup> However, since peripheral vascular resistance diminishes markedly during upright exercise, the change in pressure underestimates the inotropic reserve of the ventricle.<sup>13</sup>

#### Clinical implications

From our data, we conclude that among patients evaluated for chest pain who develop hypotension during an exercise test, coronary artery disease is not the usual underlying pathology in females. Males on the other hand have a higher incidence of coronary artery disease. However, the extent and distribution of their disease appears to be no different from that of patients without hypotension. It should be reiterated that the purpose of this study was to clarify the underlying pathology present in patients with hypotension, and no attempt was made to identify the physiologic mechanisms that

led to this abnormal response. Further studies with hemodynamic monitoring during exercise testing are warranted.

#### Summary

The significance of hypotension developing during treadmill exercise testing was evaluated and correlated with the findings at cardiac catheterization in two groups of patients. Twenty-five patients (Group I) had a fall in systolic pressure during exercise and were compared to 50 consecutive unselected patients (Group II) with a normal blood pressure response. Clinical characteristics were similar in both groups. Females comprised 48 per cent of the patients in Group I and only 30 per cent in Group II. The incidence of significant coronary artery disease was not different when the two groups were compared as a whole: 56 per cent in Group I and 36 per cent in Group II ( $P = NS$ ). When males and females were considered separately, it was noted that the incidence of coronary artery disease was higher in hypotensive males (77 per cent) when compared to control males (40 per cent) ( $p < 0.01$ ). Females in both groups had a lower but comparable incidence of coronary artery disease (25 per cent and 27 per cent, respectively). Resting hemodynamics and angiographic characteristics such as contraction abnormalities and the number and distribution of diseased coronary vessels, were similar in both groups of patients. These findings suggest that hypotension in females does not necessarily connote coronary artery disease. Males with hypotension have a higher incidence of coronary artery disease, but the extent and distribution of their disease is no different from that of patients with a normal blood pressure response to exercise.

We wish to acknowledge the technical assistance of Drs Charles Bemis, Abdulmasih Iskandran, and Demetrios Lambros for performing and interpreting the catheterization studies.

#### REFERENCES

1. Patterson J, Naughton J, Pietras R, and Connor R. Treadmill exercise in assessment of functional capacity of patients with cardiac disease. *Am J Cardiol* 30:757, 1972.
2. Bruce R, Kusumoto F, and Hoerner D. Maximal oxygen intake and hemographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 85:546, 1973.
3. Bruce R, A. Cobb L, A., Bhatnagar S, Morledge J H.

Table I Mean carboxyhemoglobin levels in the control periods before and after breathing CO and before and after breathing compressed purified air and mean ventricular fibrillation threshold (VFT) in the control periods after breathing CO and after breathing compressed purified air

|   | Control         | Before CO       | After CO        | Control         | Before compressed purified air | After compressed purified air |
|---|-----------------|-----------------|-----------------|-----------------|--------------------------------|-------------------------------|
| Mean carboxyhemoglobin level $\pm 1$ standard deviation (%)                       | 1.08 $\pm$ 0.36 | 1.11 $\pm$ 0.34 | 6.34 $\pm$ 0.53 | 1.16 $\pm$ 0.34 | 1.18 $\pm$ 0.37                | 1.07 $\pm$ 0.38               |
| Mean ventricular fibrillation threshold $\pm 1$ standard deviation (milliamperes) | 12.8 $\pm$ 6.8  |                 | 81 $\pm$ 3.8    | 11.2 $\pm$ 6.0  |                                | 15.0 $\pm$ 5.1                |

with a 182 Co Oximeter. The ventricular fibrillation threshold was then determined.

The amplified ECG potentials from the Grass recorder were fed into a triggering circuit whose output was coupled to an opto-isolator. The output from the opto-isolator was connected to a constant current stimulator. The output of the stimulator was connected to a bipolar electrode constructed of two silver tabs 5 mm in diameter each with a 4 cm separation.

The electrodes of the stimulator were placed over the same region of myocardial injury during each moment of stimulation. Test shocks were applied to the vulnerable period and were delivered every 10 seconds for 30 msec. A shock of given amplitude was repeated three times before the current was increased at increments of 1 milliamperes until ventricular fibrillation ensued. The current just adequate to provoke ventricular fibrillation was interpreted as the ventricular fibrillation threshold. After ventricular fibrillation occurred this was treated by defibrillation. A 30 minute waiting period next ensued.

Blood was then taken from the femoral artery and analyzed for carboxyhemoglobin and hemoglobin. After this the dogs breathed from a tank in a randomized blind study either 100 ppm of CO for 2 hours or compressed purified air for 2 hours. Eleven dogs were randomized to CO inhalation and 10 dogs to compressed purified air inhalation.

Two hours after either CO or compressed, purified air was breathed femoral arterial blood was drawn and analyzed for carboxyhemoglobin and hemoglobin. The ventricular fibrillation threshold was then again determined.

## Results

One of 21 dogs (5 per cent) developed spontaneous ventricular fibrillation 100 minutes after breathing CO.

Table I indicates the mean arterial carboxyhemoglobin level  $\pm 1$  standard deviation in the control periods before and after breathing CO and before and after breathing compressed purified air. The mean arterial carboxyhemoglobin level significantly increased after CO inhalation ( $t = 31.26$   $P < 0.001$ ) and significantly decreased after compressed purified air ( $t = 2.70$   $P < 0.025$ ).

Table I also shows the mean ventricular fibrillation threshold  $\pm 1$  standard deviation in the control periods after breathing CO and after breathing compressed purified air. In comparison to breathing compressed purified air CO inhalation caused a significant decrease in ventricular fibrillation threshold ( $t = 4.25$   $P < 0.001$ ).

## Discussion

The increased ventricular fibrillation threshold after breathing compressed purified air may be attributed to increased electrical stability of the injured myocardium 3 hours 20 minutes after acute myocardial injury compared to 30 minutes after acute myocardial injury. The decreased ventricular fibrillation threshold after breathing sufficient CO to raise the mean arterial carboxyhemoglobin level to 6.34 per cent may be attributed to increased myocardial ischemia lowering the ventricular fibrillation threshold. Extension of the area of myocardial injury by the increased hypoxia after CO and depression of myocardial contractility by the CO may also



# Carbon monoxide and ventricular fibrillation threshold in dogs with acute myocardial injury\*

Wilbert S Aronow, M D \*\*  
Edward A Stemmer, M D \*\*\*  
Byron Wood M D \*\*\*\*  
Stephen Zweig, M D \*\*\*\*\*  
Ke ping Tsao, M D \*\*\*\*\*  
Louis Raggio\*\*\*\*\*

Long Beach and Irvine Calif

Exposure of carbon monoxide (CO) in concentrations found during heavy atmospheric CO pollution impairs cardiovascular function in patients with cardiovascular disease<sup>1,7</sup> or in normal subjects<sup>8,10</sup> Cohen and associates also found an association between atmospheric CO pollution in Los Angeles and case fatality rates in patients with acute myocardial infarction admitted to 35 Los Angeles hospitals

DeBias and associates<sup>12</sup> showed that in monkeys with experimental myocardial infarction a greater degree of myocardial ischemia occurred in monkeys exposed to 100 p.p.m. of CO than in those breathing room air DeBias<sup>13</sup> also measured the ventricular fibrillation threshold in five monkeys with experimental myocardial infarction who breathed 100 p.p.m. of CO for 6

hours and in four monkeys with experimental myocardial infarction who breathed ambient air DeBias observed<sup>13</sup> that CO inhalation to raise the mean arterial carboxyhemoglobin level to  $102 \pm 18$  per cent was a significant factor in enhancing ventricular fibrillation in monkeys with acute myocardial infarction

We investigated the effect of breathing in a blind randomized study either 100 p.p.m. of CO or compressed purified air for 2 hours on ventricular fibrillation threshold in 21 dogs with experimental acute myocardial injury The data from this study are presented in this report

## Methods

Dogs were anesthetized with intravenous pentobarbital 45 mg /Kg and connected through an endotracheal tube with a volume controlled Harvard Pump Respirator Catheters were inserted into the right femoral artery and vein Lead II of an electrocardiogram (ECG) and the right femoral arterial pressure were recorded on a Grass Model 7 Polygraph recorder

Experimental acute myocardial injury was induced in the dogs by ligation of the left anterior descending coronary artery just distal to the first diagonal branch<sup>14</sup> An ECG verified the presence of acute myocardial injury in all dogs The area of myocardial injury demonstrated bluish discoloration and paradoxical motion in all dogs After a 30 minute wait, the following protocol was performed in 21 surviving dogs

Blood was drawn from the femoral artery and analyzed for carboxyhemoglobin and hemoglobin

From the Cardiovascular Section Medical Service and Surgical Service Long Beach Veterans Administration Hospital and the University of California College of Medicine Irvine

Received for publication May 12 1977

Accepted for publication July 18 1977

Reprint requests Wilbert S Aronow MD Chief Cardiovascular Section Veterans Administration Hospital Long Beach Calif 90822

Presented at the Annual Meeting of the American Physiological Society in Chicago on April 19 1977

Chief, Cardiovascular Section and Assistant Chief of Medicine for Research Long Beach Veterans Administration Hospital Professor of Medicine Professor of Medical Pharmacology and Therapeutics Professor of Community and Environmental Medicine Vice Chief Cardiovascular Division and Chief Cardiovascular Research University of California Irvine

Chief Surgical Service Long Beach Veterans Administration Hospital Professor of Surgery University of California Irvine

Resident in Surgery University of California Irvine

Research Cardiology Technologist Long Beach Veterans Administration Hospital

## late postoperative graft phlebitis: A rare of saphenous vein-coronary artery failure

vein coronary artery bypass graft  
great success in the symptomatic  
of angina pectoris. Postoperative  
have demonstrated that the  
rate is approximately 80 to 90 per  
the first year.<sup>1</sup> Graft occlusion  
leads at the graft to coronary artery  
disease and is due to technical failures  
of the intrinsic coronary artery  
coronary artery dissection.<sup>2</sup> Thus  
is an unusual form of saphenous  
occlusion due to a postoperative bacte-

was performed and showed a left ventricular (LV) pressure of 110/0-4 mm Hg with an LV end-diastolic pressure that rose to 18 mm Hg after contrast, and a right ventricular (RV) pressure of 10/0-12 mm Hg. Coronary arteriography showed a 70 to 90 per cent narrowing of the proximal left anterior descending coronary artery, total obstruction of the left circumflex, and a > 90 per cent proximal narrowing of the right coronary artery with multiple distal narrowings. Left ventriculogram showed good overall LV contractility. Ejection fraction was calculated at 60 per cent. Because of persistent rest pain without enzyme changes, he underwent a saphenous vein coronary artery bypass operation. A saphenous vein bypass was placed in his left anterior descending coronary artery but exploration of the right coronary artery showed it to be anastomotic for bypass. Methicillin in doses of 2 grams per day was administered 24 hours before surgery and was continued for 5 days afterwards.

Postoperatively the patient developed respiratory difficulties, gastrointestinal bleeding, and a mediastinal wound infection with *Paraclostridium aerogenes*. Despite surgical debridement and appropriate antibiotic therapy with adequate blood levels of gentamicin tested against his organism *in vitro*, he continued to do poorly, with spiking fevers, hypotension and bleeding from his mediastinal wound, and he died three weeks after the initial operation.

A autopsy of the mediastinum was open. Grossly purulent material and extensive organizing fibrinous adhesions were present in the anterior mediastinum and adjacent pericardium. The heart weighed 450 grams and a purulent pericarditis involved its anterior surface. The pericardial sac contained 130 ml of bloody fluid (collected posteriorly). The saphenous vein bypass graft to the distal left anterior descending coronary artery was also covered by shaggy adhesions. Postmortem coronary arteriography of the graft and intrinsic coronary arteries demonstrated total occlusion of the vein graft (Fig. 1). Only the first few millimeters of the distal portion of the anastomosis filled retrogradely through the left anterior descending coronary artery. The native coronary arteries had > 75 per cent proximal narrowings of the left anterior descending and right coronary arteries, and total occlusion of the left circumflex coronary artery by atherosclerotic plaque. The myocardium was hypertrophied with a wall thickness of up to 1.4 cm. A transmural scar was present

case was in good health until four years  
when he suffered an acute anterolateral  
myocardial infarction complicated by ventricular fibrillation.  
He did well, however except for mild exertional  
pain before death he developed unstable angina  
and attacks of rest pain and was admitted to  
Johns Hopkins. Pertinent physical findings on  
admission: blood pressure of 110/70 mm Hg, clear  
lungs, 2.6 systolic ejection precordial murmur  
at apex. Chest radiograph showed a normal-sized  
heart, gram, new ST depression in Leads 2, 3,  
and increased during worsening pain. Cardiac  
enzymes normal.  
In the late condition, cardiac catheterization

Medical Divisions of the Department of Medicine and  
Laboratory, The Johns Hopkins Medical Center,  
Baltimore, Md.

Received April 1, 1977  
Received May 1, 1977

Dr. Bernadine H. Bullock, Cardiovascular Div-  
ision, Johns Hopkins Medical Center, Baltimore, Md. 21205.

have contributed to the decreased ventricular fibrillation threshold after CO inhalation

The data from this blind randomized study are of public health importance as the concentration of CO used may be encountered with heavy atmospheric CO pollution (peak freeway traffic) or with smoking. The data are also compatible with the increased incidence of sudden death in patients with coronary heart disease who are heavy cigarette smokers.<sup>15</sup>

### Summary

In a blind, randomized study, the effect of breathing 100 ppm of CO versus compressed, purified air for 2 hours on ventricular fibrillation threshold (VFT) was investigated in 21 dogs with acute myocardial injury. The mean arterial carboxyhemoglobin was 1.16 per cent in the air control period, 1.07 per cent after air, 1.08 per cent in the CO control period, and 6.34 per cent after CO. In comparison to air, CO increased the mean arterial carboxyhemoglobin ( $P < 0.001$ ). One dog developed spontaneous ventricular fibrillation 100 minutes after CO. Mean VFTs in the other 20 dogs were  $12.8 \pm 6.8$  milliamperes in the CO control period,  $8.1 \pm 3.8$  milliamperes after CO,  $11.2 \pm 6.0$  milliamperes in the air control period, and  $15.0 \pm 5.1$  milliamperes after air. In comparison to air, CO decreased the VFT ( $P < 0.001$ ). These data show that breathing 100 ppm of CO for 2 hours reduces the VFT in dogs with acute myocardial injury.

### REFERENCES

1. Ayres S M, Gianelli S Jr and Mueller H S. Effects of low concentrations of carbon monoxide. Myocardial and systemic responses to carboxyhemoglobin. *Ann N Y Acad Sci* 147:268 1970
2. Aronow W S and Rokaw S N. Carboxyhemoglobin caused by smoking non nicotine cigarettes: effects in angina pectoris. *Circulation* 44:782 1971
3. Aronow W S, Harris C N, Isbell M W, Rokaw S N and Imperato J. Effect of freeway travel on angina pectoris. *Ann Intern Med* 77:669 1972
4. Anderson E W, Andelman R J, Strauch J M, Fortum N J and Knelson J M. Effect of low level carbon monoxide exposure on onset and duration of angina pectoris. A study of ten patients with ischemic heart disease. *Ann Intern Med* 79:46 1973
5. Aronow W S and Isbell M W. Carbon monoxide effect on exercise induced angina pectoris. *Ann Intern Med* 79:392 1973
6. Aronow W S, Stemmer E A and Isbell M W. Effect of carbon monoxide exposure on intermittent claudication. *Circulation* 49:415 1974
7. Aronow W S, Cassidy J, Vangrow J S, March H, Kern J C, Goldsmith J R, Khemka M, Pagano J and Vawter M. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. *Circulation* 60:340 1974
8. Ekblom B and Huor R. Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. *Acta Physiol Scand* 86:474 1972
9. Drinkwater H L, Raven P H, Horvath S M, Gliner J A, Ruhling H O, Bolduan N W and Taguchi S. Air pollution, exercise and heat stress. *Arch Environ Health* 28:177 1974
10. Aronow W S and Cassidy J. Effect of carbon monoxide on maximal treadmill exercise. A study in normal persons. *Ann Intern Med* 83:496 1975
11. Cohen S I, Duan M and Goldsmith J H. Carbon monoxide and survival from myocardial infarction. *Arch Environ Health* 19:510 1969
12. DeBus D A, Banerjee C M, Burkhead N C, Herrer W V and Kazel L A. Carbon monoxide inhalation effects following myocardial infarction in monkeys. *Arch Environ Health* 27:161 1973
13. DeBus D A. Effect of carbon monoxide inhalation on the vulnerability of the heart to induced fibrillation. In: *Clinical implications of air pollution research*. American Medical Association Air Pollution Medical Research Conference, December 5-6 1974. Acton Mass 1975. Publishing Sciences Group Inc p 119
14. Shumway N E, Johnson S A and Stish R J. The study of ventricular fibrillation by threshold determinations. *J Thorac Surg* 34:643 1957
15. The Health Consequences of Smoking. A report to the Surgeon General 1971. Washington D C 1971. U S Department of Health Education and Welfare p 38

## Acute postoperative graft phlebitis A rare cause of saphenous vein-coronary artery bypass failure

Bernadine H Bulkley, MD  
Grover M Hutchins, MD  
Baltimore, Md

Saphenous vein coronary artery bypass graft surgery has had great success in the symptomatic treatment of angina pectoris. Postoperative angiographic studies have demonstrated that the graft patency rate is approximately 80 to 90 per cent within the first year.<sup>1</sup> Graft occlusion usually develops at the graft to coronary artery anastomosis site and is due to technical failures, compression of the intrinsic coronary artery, thrombosis, or coronary artery dissection.<sup>2-4</sup> This report describes an unusual form of saphenous vein graft occlusion due to a postoperative bacterial phlebitis.

### Case report

A 6 year-old male was in good health until four years before his death when he suffered an acute anterolateral myocardial infarction complicated by ventricular fibrillation. Subsequently he did well, however except for mild exertional angina. Four weeks before death he developed unstable angina with multiple daily attacks of rest pain and was admitted to The Johns Hopkins Hospital. Pertinent physical findings on admission included a blood pressure of 110/70 mm Hg, clear lung fields, a Grade 2/6 systolic ejection precordial murmur and an S<sub>4</sub> gallop. Chest radiograph showed a normal sized heart and electrocardiogram new ST depression in Leads 2, 3, F<sub>4</sub> V<sub>1</sub> to V<sub>4</sub> that increased during worsening pain. Cardiac enzymes were normal.

Because of his unstable condition cardiac catheterization

was performed and showed a left ventricular (LV) pressure of 118/0-8 mm Hg with an LV end-diastolic pressure that rose to 18 mm Hg after contrast and a right ventricular (RV) pressure of 25/0-5 mm Hg. Coronary arteriography showed a 70 to 90 per cent narrowing of the proximal left anterior descending coronary artery, total obstruction of the left circumflex and a > 90 per cent proximal narrowing of the right coronary artery with multiple distal narrowings. Left ventriculogram showed good over all LV contractility. Ejection fraction calculated at 68 per cent. Because of persistent rest pain without enzyme changes, he underwent a saphenous vein coronary artery bypass operation. A saphenous vein bypass was placed in his left anterior descending coronary artery but exploration of the right coronary artery showed it to be unsatisfactory for bypass. Methicillin in doses of 2 grams per day was administered 24 hours before surgery and was continued for 3 days afterwards.

Postoperatively the patient developed respiratory difficulties, gastrointestinal bleeding and a mediastinal wound infection with *Pseudomonas aeruginosa*. Despite surgical débridement and appropriate antibiotic therapy with adequate blood levels of gentamycin tested against his organism in vitro, he continued to do poorly with spiking fevers, hypotension and bleeding from his mediastinal wound and he died three weeks after the initial operation.

At autopsy the mediastinum was open. Grossly purulent material and extensive organizing fibrous adhesions were present in the anterior mediastinum and adjacent pericardium. The heart weighed 490 grams, and a purulent pericarditis involved its anterior surface. The pericardial sac contained 100 ml. of bloody fluid loculated posteriorly. The saphenous vein bypass graft to the distal left anterior descending coronary artery was also covered by shaggy adhesions. Postmortem coronary arteriography of the graft and intrinsic coronary arteries demonstrated total occlusion of the vein graft (Fig 1). Only the first few millimeters of the distal portion of the anastomosis filled retrogradely through the left anterior descending coronary artery. The native coronary arteries had > 75 per cent proximal narrowings of the left anterior descending and right coronary arteries, and total occlusion of the left circumflex coronary arteries by atherosclerotic plaque. The myocardium was hypertrophied with a wall thickness of up to 1.6 cm. A transmural scar was present

From the Cardiovascular Division of the Department of Medicine and the Department of Pathology, The Johns Hopkins Medical Institution, Baltimore, Md.

Supported by Grant P50-HL-17855-03 with The National Institutes of Health, Public Health Service, Department of Health, Education and Welfare and the Stetler Research Fund of the Veterans Physicians.

Received for publication April 8, 1977.  
Accepted for publication May 17, 1977.

Reprint requests to Dr. Bernadine H. Bulkley, Cardiovascular Division, The Johns Hopkins Hospital, Baltimore, Md. 21205.

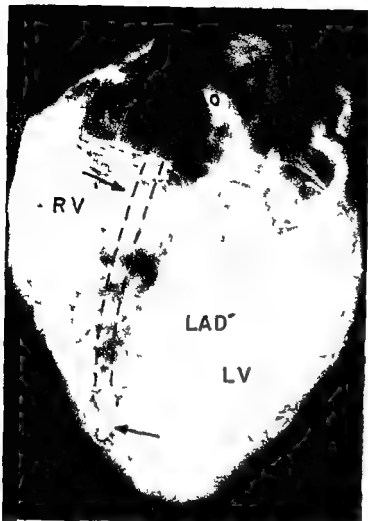


Fig 1 Postmortem coronary arteriogram showing course of occluded saphenous vein graft (dotted lines). Only the terminal portion of the graft at the anastomosis of the saphenous vein graft to the left anterior descending (LAD) coronary artery (lower arrow) contains infection mass. The intramural abscess is located at upper arrow. Ao = aorta, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

in the apical inferior left ventricular myocardium and foci of fibrosis were present in the posterior wall. Histologic examination of the myocardium demonstrated focal areas of organizing contraction band necrosis indicative of reperfusion of transiently unperfused myocardium but no areas of recent coagulation necrosis.

Serial histologic sectioning of the graft to artery anastomosis site demonstrated a widely patent anastomosis (Fig 2) and as suggested from gross examination and postmortem angiography within approximately a few millimeters of the anastomosis an occlusive organizing thrombus was present in the vein graft. At the junction of proximal and middle thirds of the graft the wall of the vein was focally necrotic and infiltrated with polymorphonuclear leukocytes (Fig 3). The intramural abscess appeared to be the origin of the thrombus which occluded almost all of the graft. Overlying the vein graft was an organizing purulent epicarditis. The portion of the vein immediately adjacent to the coronary artery anastomosis was free of thrombus and was not infected. The proximal (aorta to vein) anastomosis was intact.

## Discussion

This 67 year old man with unstable angina died three weeks after operation of bleeding and sepsis related to a *Pseudomonas* mediastinitis. An unexpected and previously unreported finding at autopsy was thrombosis of a coronary artery saphenous vein bypass graft due to graft phlebitis. Although late occlusions may result from fibrous intimal proliferation,<sup>9, 10</sup> most early graft occlusions are related to technical problems at the anastomosis site including anastomoses into vessels of too small a caliber, or ones with distal disease and poor runoff. Thrombosis of the graft is frequently associated with thrombosis of the intrinsic coronary artery at the site of anastomosis.<sup>9</sup> In this patient, however, early graft failure occurred in the presence of a widely patent technically good anastomosis and thrombosis of the graft did not progress to thrombosis of the grafted coronary artery. Thus, although the possible benefit intended from the bypass graft was not obtained without a new intrinsic coronary occlusion or narrowing, his myocardial coronary perfusion was not worsened by the graft failure. Consistent with this, at autopsy there was no evidence of a myocardial infarction related to the graft failure.

Isolated graft occlusion in this patient was related to graft infection. The organizing thrombus arose from a severe acute phlebitis with a mural abscess in the vein graft. Although coronary artery bypass operations involve a limb dissection and a fair amount of manipulation of tissue prior to implantation, graft infection is a virtually unheard of complication of this procedure. The phlebitis in the patient studied here was associated with a severe purulent mediastinitis and pericarditis. It is most likely that mediastinitis led to pericarditis and subsequently phlebitis. That an infected vein graft might have led to an overlying purulent pericarditis and mediastinitis is also possible. Mediastinitis has been associated with prosthetic valve endocarditis and in some instances which infected site was the initiator of infection is not clear.<sup>11</sup>

Although mediastinitis is not an infrequent postoperative complication, purulent mediastinitis and even purulent pericarditis are not necessarily associated with graft phlebitis. We have studied one other patient with purulent pericarditis after a double coronary artery bypass graft.

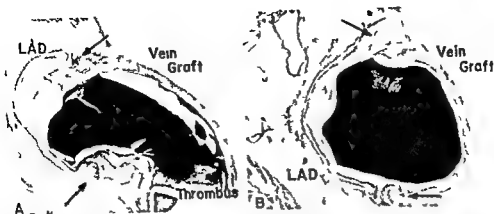


Fig 2 A and B Selected serial histologic sections of the saphenous vein graft to left anterior descending (LAD) anastomosis (lower arrow in Fig 1) A Through the graft and opened artery showing end of thrombus in the vein graft and dark staining infection mass in terminal graft and artery. The suture line is at the arrows and an atheroma is within the artery but the anastomosis is widely patent B Distal to A showing the open artery (below) roofed by vein graft (above). The arrows show the suture line (Both Verhoeff van Gieson stain original magnification  $\times 15$ )

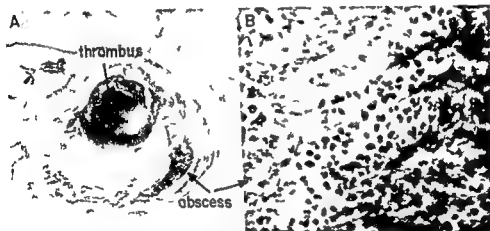


Fig 3 A and B A Transverse section of vein graft at the upper arrow of Fig 1 showing thrombotic occlusion of the lumen related to an intramural abscess (Hematoxylin and eosin stain original magnification  $\times 15$ ) B Margin of abscess shown in A demonstrating purulent exudate (Hematoxylin and eosin stain original magnification  $\times 450$ )

operation and neither of his grafts became infected. Nevertheless the mediastinal and pericardial infection of this patient who failed to respond to standard therapy may have been a clue to the infectious involvement of the unimplanted graft. Particularly in the setting of a completely thrombosed vessel it is probable that eradication of infection would have required removal of the infected vein.

Cardiac infection after heart operations are not common but when they occur the consequences are devastating and generally successful outcome requires prompt surgical intervention. It is

important to recognize therefore that saphenous vein grafts like prosthetic valves and septal defect patches can become infected and that such infection may be a cause of thrombosis and occlusion.

#### Summary

Most graft occlusions occurring early after saphenous vein coronary artery bypass procedures result from technical problems at the graft to coronary artery anastomosis site. This report describes an unusual cause of graft occlusion in a 67 year old man who died three weeks

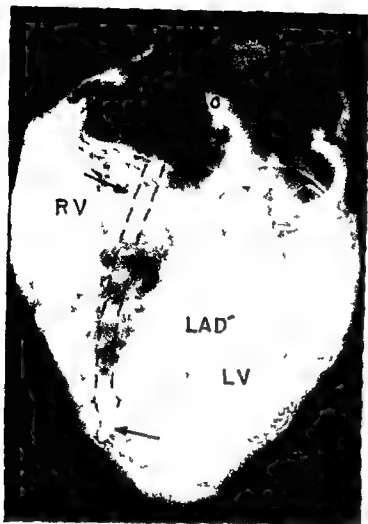


Fig 1 Postmortem coronary arteriogram showing course of occluded saphenous vein graft (dotted lines). Only the terminal portion of the graft at the anastomosis of the saphenous vein graft to the left anterior descending (LAD) coronary artery (lower arrow) contains infection mass. The intramural abscess is located at upper arrow. Ao = aorta, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

in the apical inferior left ventricular myocardium and foci of fibrosis were present in the posterior wall. Histologic examination of the myocardium demonstrated focal areas of organizing contraction band necrosis indicative of reperfusion of transiently unperfused myocardium, but no areas of recent coagulation necrosis.

Serial histologic sectioning of the graft to artery anastomosis site demonstrated a widely patent anastomosis (Fig 2) and as suggested from gross examination and postmortem angiography within approximately a few millimeters of the anastomosis an occlusive organizing thrombus was present in the vein graft. At the junction of proximal and middle thirds of the graft the wall of the vein was focally necrotic and infiltrated with polymorphonuclear leukocytes (Fig 3). The intramural abscess appeared to be the origin of the thrombus which occluded almost all of the graft. Overlying the vein graft was an organizing purulent epicarditis. The portion of the vein immediately adjacent to the coronary artery anastomosis was free of thrombus and was not infected. The proximal (aorta to vein) anastomosis was intact.

## Discussion

This 67 year old man with unstable angina died three weeks after operation of bleeding and sepsis related to a *Pseudomonas* mediastinitis. An unexpected and previously unreported finding at autopsy was thrombosis of a coronary artery saphenous vein bypass graft due to graft phlebitis. Although late occlusions may result from fibrous intimal proliferation,<sup>10</sup> most early graft occlusions are related to technical problems at the anastomosis site including anastomoses into vessels of too small a caliber, or ones with distal disease and poor runoff. Thrombosis of the graft is frequently associated with thrombosis of the intrinsic coronary artery at the site of anastomosis.<sup>11</sup> In this patient however, early graft failure occurred in the presence of a widely patent technically good anastomosis and thrombosis of the graft did not progress to thrombosis of the grafted coronary artery. Thus, although the possible benefit intended from the bypass graft was not obtained without a new intrinsic coronary occlusion or narrowing, his myocardial coronary perfusion was not worsened by the graft failure. Consistent with this at autopsy, there was no evidence of a myocardial infarction related to the graft failure.

Isolated graft occlusion in this patient was related to graft infection. The organizing thrombus arose from a severe acute phlebitis with a mural abscess in the vein graft. Although coronary artery bypass operations involve a limb dissection and a fair amount of manipulation of tissue prior to implantation, graft infection is a virtually unheard of complication of this procedure. The phlebitis in the patient studied here was associated with a severe purulent mediastinitis and pericarditis. It is most likely that mediastinitis led to pericarditis and subsequently phlebitis. That an infected vein graft might have led to an overlying purulent pericarditis and mediastinitis is also possible. Mediastinitis has been associated with prosthetic valve endocarditis and in some instances which infected site was the initiator of infection is not clear.<sup>12</sup>

Although mediastinitis is not an infrequent postoperative complication, purulent mediastinitis and even purulent pericarditis are not necessarily associated with graft phlebitis. We have studied one other patient with purulent pericarditis after a double coronary artery bypass graft.

# Simulated tricuspid valve echoes in tricuspid atresia

Norman H Silverman M D

Maurice Payot M D \*

Paul Stanger M D

San Francisco Calif

Echocardiography is most valuable in the assessment of neonates with hypoplastic right heart complexes. While a tricuspid valve echo is usually present in hypoplastic right heart complexes associated with pulmonary atresia, the absence of this echo strongly favors tricuspid atresia. This communication documents a case of tricuspid atresia proven by catheterization and necropsy in which the echocardiogram showed echoes strongly resembling those of a tricuspid valve

## Case report

This two-day-old male infant weighed 3.5 kilograms at birth. Cyanosis, tachypnea and a heart murmur were detected shortly after birth. Umbilical arterial blood gas analyses showed a PO of 38 torr, a PCO of 24 torr and a pH of 7.38 while breathing room air, while breathing 100 per cent oxygen the PO rose to 57 torr. He subsequently developed signs of poor perfusion and acidosis and was transferred to our institution for further evaluation.

Physical examination showed a full term baby with tachypnea, mild hyperpnea, central cyanosis and decreased peripheral perfusion. The peripheral pulses were barely palpable in all extremities. The heart rate was 140 beats/minute, the respiratory rate 100/minute. The descending aortic blood pressure measured by an umbilical arterial catheter was 60/40 (mean 48) mm Hg. A diffuse precordial impulse was felt. The first heart sound was normal and the second sound single. There was a Grade 4/6 short systolic ejection murmur which was loudest at the mid left sternal border. The liver edge was palpated 5 cm below the right costal margin and the spleen tip was 2 cm below the left costal margin. Umbilical arterial blood gas analysis showed a pH of 6.99, a PCO of 25 torr and

a PO of 64 torr. An electrocardiogram showed sinus tachycardia, a mean frontal plane QRS axis of +60 degrees and decreased right ventricular forces. A chest roentgenogram showed moderate cardiomegaly with normal pulmonary vascular markings.

The clinical impression was that the child had a cardiac anomaly resulting in cyanosis and obstruction to left ventricular outflow. The diagnoses considered most likely were transposition of the great arteries with tricuspid atresia and a restrictive ventricular septal defect or transposition with a hypoplastic right ventricle.

An echocardiogram was obtained from the standard positions (see Figs 1 and 3). Fig 1 demonstrates an M-mode sweep from the valve of the posterior great artery through the posterior atrioventricular valve. The anterior wall of the posterior great artery was continuous with the ventricular septum and the artery's posterior wall was continuous with the anterior leaflet of the mitral valve. The latter lay posteriorly and leftward. These findings were consistent with a ventricular loop. On pivoting the transducer cranially and rightward a smaller arterial root (aorta) was identified. The valve leaflets of this artery were poorly defined and the arterial root lay anterior to the valve of the larger, more posterior great artery. The interrelationship of the arterial roots was typical for d transposition (see Fig 2). During the study a 2:1 atrioventricular block developed, however the atrial contraction that occurred early in diastole had no perceptible effect on the mitral valve motion (Fig 3a). On pivoting the transducer to the region of the tricuspid valve an echo pattern was seen that was interpreted as tricuspid valvular in origin (Fig 3b). Although the apparent valve motion was of a lesser amplitude than that of the mitral valve, the timing of the "E" and "A" points was similar to that of the mitral valve echo. These echocardiographic patterns could only be recorded during the latter part of the study when 2:1 atrioventricular block was present. The echocardiogram was interpreted as being compatible with transposition of the great arteries with a diminutive right ventricle and hypoplastic ascending aorta. We thought that we had excluded tricuspid atresia because of the recording of echoes emanating from a structure which appeared to be a tricuspid valve. Cardiac catheterization was performed and demonstrated d transposition of the great arteries, tricuspid atresia, a diminutive right ventricle, a restrictive ventricular septal defect and interrupted

From the Cardiovascular Research Institute and the Department of Pediatrics, University of California, San Francisco, Calif.  
Received for publication June 10, 1977.

Accepted for publication July 1, 1977.

Reprint requests: Norman H Silverman, MD, 1400 HSE, University of California, San Francisco, Calif 94143.

\*Supported by research grant from the San Francisco Bay Area Heart Association.

0007-1226/78/0005-0061\$01.50/0 © 1978 The C V Mosby Co



after operation—a postoperative acute phlebitis of an implanted saphenous vein graft. Infection in the graft wall resulted in isolated graft thrombosis in the setting of a patent anastomosis. Graft phlebitis in this patient was associated with a purulent pericarditis and mediastinitis which failed to respond to surgical débridement and antibiotic therapy. Although mediastinitis is not infrequent, infection of an implanted saphenous vein coronary artery bypass graft in association with mediastinitis has never been reported. The findings in our case show that such graft infection may occur and may result in graft thrombosis and occlusion.

# REFERENCES

- 1 Spencer F C, Green G E, Tice D A and Glassman E. Bypass grafting for occlusive disease of the coronary arteries: a report of experience with 195 patients. *Ann Surg* 173:1029, 1971.
- 2 Bourassa M G, Goulet C and Lesperance J. Progression of coronary arterial disease after aortocoronary bypass grafts. *Circulation* 47 and 48 (Suppl. III):127, 1973.
- 3 Alderman E L, Matloff H J and Wexler L. Results of direct coronary-artery surgery for treatment of angina pectoris. *N Engl J Med* 288:535, 1973.
- 4 Bonchek L I, Rahmtools S H, Chaitman B R, Rosch J, Anderson R P and Starr A. Vein graft occlusion: Immediate and late consequences and therapeutic implications. *Circulation* 49 and 50 (Suppl. II):II, 1974.
- 5 Morris D C Jr, Reul G J, Howell J F, Crawford E S, Chapman D W., Beazley H L, Winters, W L, Peterson P K., and Lewis J M. Follow up results of distal coronary artery bypass for ischemic heart disease. *Am J Cardiol* 29:180, 1972.
- 6 Griffith L S C, Bulkley B H, Hutchins G M and Brawley R K. Occlusive changes at the coronary artery-bypass graft anastomosis. Morphologic study of 95 grafts. *J Thorac Cardiovasc Surg*, 73:668, 1977.
- 7 Hutchins G M and Anaya O A. Measurements of cardiac size, chamber volumes and valve orifices at autopsy. *Johns Hopkins Med J* 133:96, 1973.
- 8 Bulkley B H, Rudolf R L, Salyer W R and Hutchins G M. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. *Circulation* 53:483, 1976.
- 9 Unni K K., Kottke B A, Titus J L, Frye H L, Wallace R B and Brown A L. Pathologic changes in aortocoronary saphenous vein grafts. *Am J Cardiol* 34:526, 1974.
- 10 Bulkley B H and Hutchins, G M. Accelerated "atherosclerosis." A morphologic study of 97 saphenous vein coronary artery bypass grafts. *Circulation* 55:163, 1976.
- 11 Anderson D J, Bulkley B H and Hutchins G M. A clinicopathologic study of prosthetic valve endocarditis in 22 patients. Morphologic basis for diagnosis and therapy. *Am Heart J* 94:325, 1977.
- 12 Bulkley B H, Humphries J O and Hutchins G M. Purulent pericarditis with asymmetric cardiac tamponade. A cause of death months after coronary bypass surgery. *Am Heart J* 93:776, 1977.

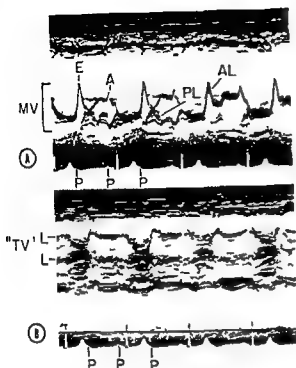


Fig 3 A and B A Top panel shows the mitral valve with anterior leaflet and posterior leaflet within a large ventricular chamber. The E and A points are shown on the mitral valve AL anterior leaflet MV mitral valve PL posterior leaflet B The bottom panel demonstrates the spurious echo located in the usual area of the tricuspid valve which mimics the tricuspid valve with anterior and posterior leaflets. Note 2:1 atrioventricular block with a ventriculophasic response is present in these two panels. The paper speed (50 mm/sec) is the same as the other examples L leaflets TV tricuspid valve

small tricuspid valve was present. Initially the motion of this echo was judged typical for an anterior atrioventricular valve including the appearance of two leaflets and seemed to satisfy all the criteria established for echoes of tricuspid valve origin. The pattern of leaflet motion was similar to that recorded for the mitral valve during second degree atrioventricular block.

As no tricuspid valve was present an alternate explanation for the apparent tricuspid echoes was sought. There are two reasons to suggest that the diastolic echo motion was the result of atrial contractions. Firstly the diastolic motion cannot be explained by ventricular free wall ventricular septal or semilunar valve motion. On reviewing the pathological specimen it was unlikely that the echoes could have originated from the right ventricle as this was minute and the distance between the walls was much less than the space between the apparent anterior and posterior

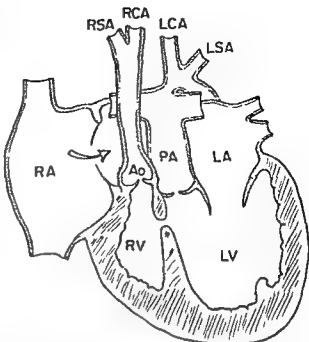


Fig 4 Pathological diagram of the patient showing tricuspid atresia ventricular septal defect and diminutive right ventricle transposition and a hypoplastic aorta an interrupted aortic arch between the innominate and right carotid arteries and a patent ductus arteriosus. The arrow indicates the direction of flow through the interatrial communication Ao aorta LA left atrium LCA left carotid artery LSA left subclavian artery LV left ventricle PA pulmonary artery RA right atrium RCA right carotid artery RSA right subclavian artery RV right ventricle

echoes of the tricuspid leaflets. Secondly the temporal relationship of the echo motion to the electrocardiographic P waves is evident that the apparent E and A points occur immediately after the P waves. That two atrial contractions should result in an apparent E as well as A excursion is undoubtedly the result of 2:1 atrioventricular block. Similarly the difference in amplitude of the E and A points is probably related to their timing in relation to the ventricular systole.

In tricuspid atresia with a large interatrial communication such as was present in this case the amplitude of the right atrial contraction would be influenced by left ventricular events. The difference in amplitude between the apparent E and A points may reflect differences at the beginning and the end of ventricular diastole.

In order to determine which atrial structures might have produced the echo pattern the necropsy specimen (Figs 5a and 5b) was examined *in situ*. The most anterior structure encountered

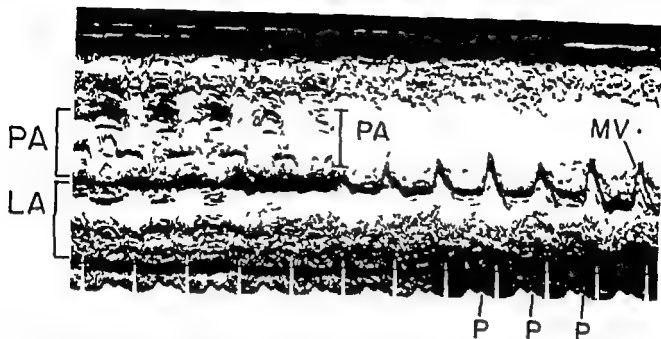


Fig 1 Echocardiogram showing a sweep from the posterior great vessel (the pulmonary artery) through the left ventricle. The left atrium identified behind the pulmonary root. The posterior pulmonary root is continuous with the mitral valve. The P waves on ECG are indicated on three of the latter complexes. LA left atrium, MV mitral valve, PA pulmonary artery.

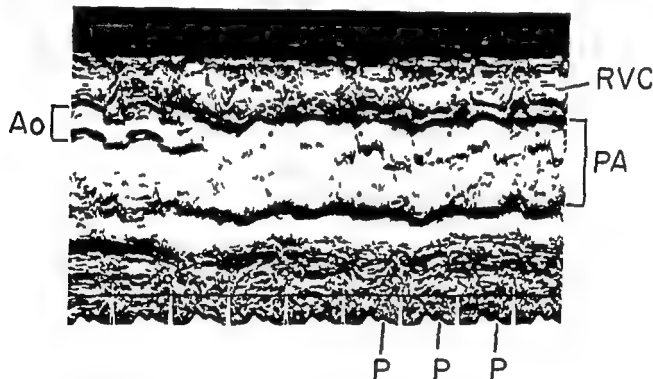


Fig 2 Echocardiogram demonstrating a sweep from the right to the left sides of the patient. A small anteroposed aorta is anterior and to the right of the pulmonary artery. On the right hand side of the figure is the right ventricular cavity. The P waves on the ECG are indicated. Ao aorta, RVC right ventricular cavity.

tion of the aortic arch between the origin of the carotid arteries. No surgical intervention was attempted and the baby subsequently died. Necropsy confirmed the diagnoses demonstrated by cardiac catheterization (Figs 4 and 5).

#### Discussion

Echocardiography has been helpful in identifying various forms of hypoplastic right heart complexes.<sup>1-4</sup> The absence of specific echoes from

the tricuspid valve leaflets in the presence of a small anterior and rightward ventricle is typical of tricuspid atresia. In contrast, the presence of a small amplitude tricuspid echo is usually associated with hypoplastic right ventricle and a small tricuspid valve. Although the clinical findings in this case strongly favored tricuspid atresia, the echocardiographic demonstration of apparent tricuspid leaflet motion led us to conclude that a

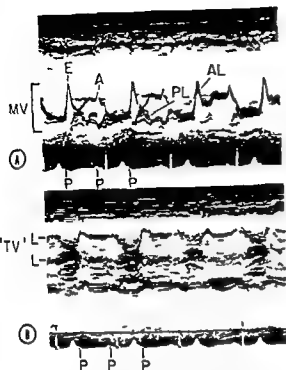


Fig 3 A and B Top panel shows the mitral valve with anterior leaflet and posterior leaflet within a large ventricular chamber. The E and A points are shown on the mitral valve. AL anterior leaflet, MV mitral valve, PL posterior leaflet. B The bottom panel demonstrates the spurious echo located in the usual area of the tricuspid valve which mimics the tricuspid valve with anterior and posterior leaflets. Note 2:1 atrioventricular block with a ventriculophasic response is present in these two panels. The paper speed (50 mm/sec) is the same as the other examples. L leaflets, TV tricuspid valve.

small tricuspid valve was present. Initially the motion of this echo was judged typical for an anterior atrioventricular valve including the appearance of two leaflets and seemed to satisfy all the criteria established for echoes of tricuspid valve origin.<sup>12</sup> The pattern of leaflet motion was similar to that recorded for the mitral valve during second degree atrioventricular block.

As no tricuspid valve was present an alternate explanation for the apparent tricuspid echoes was sought. There are two reasons to suggest that the diastolic echo motion was the result of atrial contractions. Firstly the diastolic motion cannot be explained by ventricular free wall, ventricular septal or semilunar valve motion. On reviewing the pathological specimen it was unlikely that the echoes could have originated from the right ventricle as this was minute and the distance between the walls was much less than the space between the apparent anterior and posterior

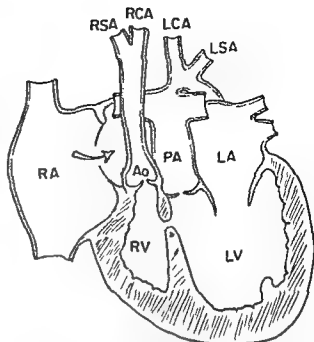


Fig 4 Pathological diagram of the patient showing tricuspid atresia, ventricular septal defect and diminutive right ventricle, transposition and a hypoplastic aorta, an interrupted aortic arch between the innominate and right carotid arteries and a patent ductus arteriosus. The arrow indicates the direction of flow through the interatrial communication. Ao aorta, LA left atrium, LCA left carotid artery, LSA left subclavian artery, LV left ventricle, PA pulmonary artery, RA right atrium, RCA right carotid artery, RSA right subclavian artery, RV right ventricle.

echoes of the tricuspid leaflets. Secondly the temporal relationship of the echo motion to the electrocardiographic P waves is evident that is the apparent E and A points occur immediately after the P waves. That two atrial contractions should result in an apparent E as well as A excursion is undoubtedly the result of 2:1 atrioventricular block. Similarly the difference in amplitude of the E and A points is probably related to their timing in relation to the ventricular systole.

In tricuspid atresia with a large interatrial communication such as was present in this case the amplitude of the right atrial contraction would be influenced by left ventricular events. The difference in amplitude between the apparent E and A points may reflect differences at the beginning and the end of ventricular diastole.

In order to determine which atrial structures might have produced the echo pattern the necropsy specimen (Figs 5a and 5b) was examined in situ. The most anterior structure encoun-

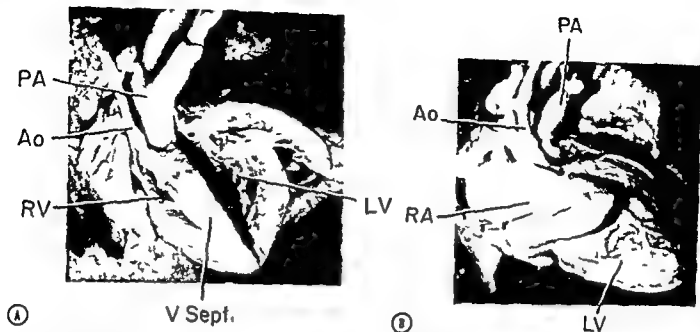


Fig 5 A and B are photographs of this pathological specimen A (left panel) shows the specimen viewed from the front as it lay in the chest B (right panel) is the dissected specimen A stick 1/8 inch in diameter just passed through the ventricular septal defect Ao aorta PA pulmonary artery RA right atrium RV right ventricle V Sept ventricular septum

tered by the echo beam was probably the right atrial appendage. It lay interposed between the chest wall and the left ventricle and consequently may have been partially responsible for the apparent tricuspid echo. It was however, unlikely to be the sole source of both apparent leaflet motions. Normally the space behind the anterior chest wall is occupied by the anterior cardiac structures a space being noted only in the presence of pericardial effusion. As no effusion was present the echo which resembles the anterior tricuspid valve leaflet could not have originated from the anterior wall of the right atrial appendage. Probably the apparent anterior leaflet echo arose from the posterior wall of the right atrial appendage and the echo resembling the posterior tricuspid leaflet arose from the inferior or posterior wall of the right atrium or the atrial septum. Alternatively, both the apparent tricuspid valve leaflet echoes may have originated from the anterior and posterior aspects of the floor of the right atrium.

The structural relationships at necropsy were such that it is unlikely that the echoes arose from the interatrial septum or the valve of the foramen ovale. Each was too posterior to have resulted in the apparent tricuspid echoes. It is conceivable that the valve of the inferior vena cava or the coronary sinus might produce similar

echo wave forms however, at necropsy both these structures were too small to have produced the recorded amplitude of motion.

Although we have advanced possible explanations for the echocardiographic findings it is possible that none of these are correct. Indocyanine green studies at the time of catheterization<sup>14</sup> might have proven useful in further defining the location of the echo but the patient's critical condition precluded such a study. For the same reasons, cross sectional echocardiography was not performed.

In hypoplastic right heart complexes it is frequently difficult to identify tricuspid valve echoes and, if found the tricuspid valve echo pattern may be quite atypical. Fig 6 illustrates such a case. The patient had a hypoplastic right ventricle and a small tricuspid valve. The echo pattern is less typical of tricuspid valve than the apparent tricuspid echoes from our patient with tricuspid atresia. The occurrence of 2:1 atrioventricular block probably led to this rare echocardiographic pattern as during the rest of the examination sinus rhythm was present.

Caution should be exercised in identifying tricuspid valve echoes in patients with hypoplastic right ventricle. Clearly failure to demonstrate a structure by echocardiography may be the result of absence of that structure or it may

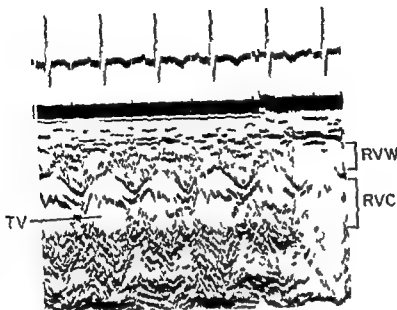


Fig 1 Echocardiogram of a patient with pulmonary atresia and a diminutive right ventricle showing the echo from the small tricuspid valve. RVC, right ventricular cavity; RVW, right ventricular wall; TV, tricuspid valve.

merely be the result of inability to locate it. On the other hand, simulation of valve motion is most unusual.

### Summary

A case of tricuspid atresia with unusual echocardiographic findings is presented. The echocardiogram was successful in defining great artery interrelationships, ventricular looping and cavity sizes. An echo pattern resembling the motion of a small tricuspid valve was observed; this was proven to be spurious at catheterization and necropsy. Caution should be exercised in diagnosing the presence of a tricuspid valve on the basis of atypical echoes from the tricuspid valve area.

The authors wish to thank Drs Harvey Feitenbaum and Richard Popp for their interest, constructive criticism and advice.

### REFERENCES

1. Chesler E, Joffe H, S. Vecht R et al. Ultrasound cardiography in single ventricle and the hypoplastic left and right heart syndromes. *Circulation* 42: 1319, 1970.
2. Chesler E, Joffe H, Beck W et al. Echocardiography in the diagnosis of congenital heart diseases. *Pediatr Clin North Am* 18: 1163, 1971.
3. Lundstrom N R. and Edler I. Ultrasound cardiography in infants and children. *Acta Paediatr Scand* 60: 117, 1971.
4. Meyer R A. and Kaplan S. Echocardiography in the diagnosis of hypoplasia of the left or right ventricle in the neonate. *Circulation* 46: 55, 1972.
5. Meyer R A. and Kaplan S. Non-invasive techniques in pediatric cardiovascular disease. *Progr Cardiovasc Dis* 40: 341, 1973.
6. Lundstrom N R. Clinical applications of echocardiography in infants and children. *Acta Paediatr Scand* (Suppl 243): 1, 1974.
7. Godmann M J, Tham P and Langford Ludd B S. Echocardiography in the evaluation of the cyanotic newborn infant. *Br Heart J* 36: 154, 1974.
8. Fibi F, Solinger R and Minhas K. Echocardiographic features of pulmonary atresia type (Abstr). *Circulation* 50 (Suppl III): 111, 1974.
9. Sahn D J, Allen H D, Goldberg S J et al. Medical progress in pediatric cardiology. A review of its clinical utility. *J Pediatr* 87: 335, 1975.
10. Riemenschneider T A, Vincent W A, Ruttenberg H D et al. Transposition of the great vessels with hypoplasia of the right ventricle. *Circulation* 38: 386, 1967.
11. Solinger R, Elbl F and Minhas K. Deductive echocardiographic analysis in infants with congenital heart disease. *Circulation* 50: 1072, 1974.
12. Gramiak R, Chung K J, Nanda N et al. Echocardiographic diagnosis of transposition of the great vessels. *Radiology* 106: 187, 1973.
13. Edler I. The diagnostic use of ultrasound in heart disease. In *Cardiology: An Encyclopedia of cardiovascular systems*, suppl. 1. Lissada A. A. ed. New York, 1969. McGraw Hill Book Company Inc.
14. Gramiak R, Shah, P M and Kramer D H. Intrasonic cardiography: contrast studies in anatomy and function. *Radiology* 92: 939, 1969.
15. Seward J B, Tappin H J, Spangler J G et al. Echocardiographic contrast studies: Initial experience. *Mayo Clin Proc* 50: 163, 1975.

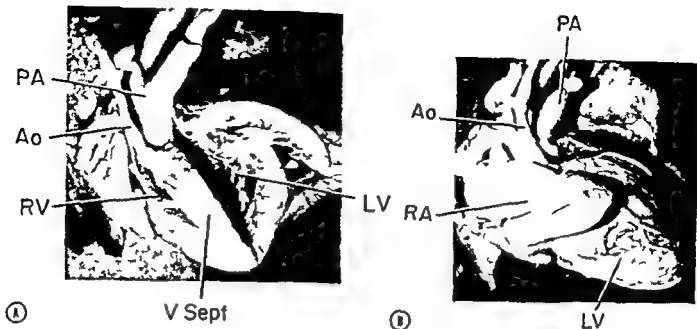


Fig 5 A and B are photographs of this pathological specimen A (left panel) shows the specimen viewed from the front as it lay in the chest B (right panel) is the dissected specimen A stick  $\frac{1}{8}$  inch in diameter just passed through the ventricular septal defect Ao aorta PA pulmonary artery RA right atrium RV right ventricle V Sept ventricular septum

tered by the echo beam was probably the right atrial appendage. It lay interposed between the chest wall and the left ventricle and consequently may have been partially responsible for the apparent tricuspid echo. It was, however, unlikely to be the sole source of both apparent leaflet motions. Normally the space behind the anterior chest wall is occupied by the anterior cardiac structures, a space being noted only in the presence of pericardial effusion. As no effusion was present, the echo which resembles the anterior tricuspid valve leaflet could not have originated from the anterior wall of the right atrial appendage. Probably the apparent anterior leaflet echo arose from the posterior wall of the right atrial appendage and the echo resembling the posterior tricuspid leaflet arose from the inferior or posterior wall of the right atrium or the atrial septum. Alternatively, both the apparent tricuspid valve leaflet echoes may have originated from the anterior and posterior aspects of the floor of the right atrium.

The structural relationships at necropsy were such that it is unlikely that the echoes arose from the interatrial septum or the valve of the foramen ovale. Each was too posterior to have resulted in the apparent tricuspid echoes. It is conceivable that the valve of the inferior vena cava or the coronary sinus might produce similar

echo wave forms, however, at necropsy both these structures were too small to have produced the recorded amplitude of motion.

Although we have advanced possible explanations for the echocardiographic findings, it is possible that none of these are correct. Indocyanine green studies at the time of catheterization<sup>14</sup> might have proven useful in further defining the location of the echo, but the patient's critical condition precluded such a study. For the same reasons, cross sectional echocardiography was not performed.

In hypoplastic right heart complexes it is frequently difficult to identify tricuspid valve echoes and if found the tricuspid valve echo pattern may be quite atypical. Fig 6 illustrates such a case. The patient had a hypoplastic right ventricle and a small tricuspid valve. The echo pattern is less typical of tricuspid valve than the apparent tricuspid echoes from our patient with tricuspid atresia. The occurrence of 2:1 atrioventricular block probably led to this rare echocardiographic pattern as during the rest of the examination sinus rhythm was present.

Caution should be exercised in identifying tricuspid valve echoes in patients with hypoplastic right ventricle. Clearly, failure to demonstrate a structure by echocardiography may be the result of absence of that structure or it may

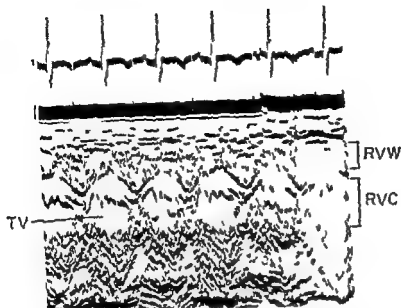


Fig. 1. Echocardiogram of a patient with pulmonary atresia and a diminutive right ventricle showing the echo from the small tricuspid valve. RVC, right ventricular cavity; RVW, right ventricular wall; TV, tricuspid valve.

merely be the result of inability to locate it. On the other hand, simulation of valve motion is most unusual.

### Summary

A case of tricuspid atresia with unusual echocardiographic findings is presented. The echocardiogram was successful in defining great artery interrelationships, ventricular looping, and cavity sizes. An echo pattern resembling the motion of a small tricuspid valve was observed; this was proven to be spurious on catheterization and necropsy. Caution should be exercised in diagnosing the presence of a tricuspid valve on the basis of atypical echoes from the tricuspid valve area.

The authors wish to thank Drs. Harvey Feigenbaum and Richard Popp for their interest, constructive criticism, and advice.

### REFERENCES

- Chesler E, Joffe H, S. Vecht R, et al. Ultrasoundcardiography in single ventricle and the hypoplastic left and right heart syndromes. *Circulation* 42:139-150.
- Chesler E, Joffe H, Beck W, et al. Echocardiography in the diagnosis of congenital heart diseases. *Pediatr Clin North Am* 18:1363-1372.
- Lundstrom N R and Edler J. Ultrasound cardiography in infants and children. *Acta Paediatr Scand* 60:117-1971.
- Meyer R A and Kaplan S. Echocardiography in the diagnosis of hypoplasia of the left or right ventricles in the neonate. *Circulation* 48:5, 1972.
- Meyer R A and Kaplan S. Non-invasive techniques in pediatric cardiovascular disease. *Progr Cardiovasc Dis* 40:341-1973.
- Lundstrom N R. Clinical applications of echocardiography in infants and children. *Acta Paediatr Scand (Suppl)* 243:1-1974.
- Godmann M J, Tham P, and Langford Add, B. Echocardiography in the evaluation of the cyanotic newborn infant. *Br Heart J* 36:154-1974.
- Elbi F, Solinger R, and Minhas K. Echocardiographic features of pulmonary atresia type (Atrial). *Circulation* 50 (Suppl III):111-1974.
- Sahn D J, Allen H D, Goldberg S J, et al. Medical progress in pediatric cardiology. A review of its clinical utility. *J Pediatr* 87:335-1975.
- Kuemenschneider T A, Vincent W A, Ruttenberg H D, et al. Transposition of the great vessels with hypoplasia of the right ventricle. *Circulation* 38:386-1967.
- Solinger R, Elbi F, and Minhas K. Deductive echocardiographic analysis in infants with congenital heart disease. *Circulation* 50:1072, 1974.
- Gramiak R, Chung K J, Nanda N., et al. Echocardiographic diagnosis of transposition of the great vessels. *Radiology* 106:187-1973.
- Edler J. The diagnostic use of ultrasound in heart disease. In: *Cardiology: an Encyclopedia of cardiovascular system* (suppl.) Lusada A A, ed. New York 1969. McGraw-Hill Book Company Inc.
- Gramiak R, Shah P M, and Kramer D H. Ultrasound cardiography: contrast studies in anatomy and function. *Radiology* 112:939-1969.
- Seward J M, Tajik H J, Spangler J G, et al. Echocardiographic contrast studies: Initial experience. *Mayo Clin Proc* 50:163-1975.



# Clinical pathologic conference

## Massive myocardial necrosis in a young woman

Rimgaudas Nemickas, M D

David Fishman, M D

Thomas Killip, M D

Willard Dalton, M D

Gissur Brynjolfsson, M D

John Robinson, M D

Rolf M. Gunnar, M D

Maywood and Evanston III

### Case presentation

DR DAVID FISHMAN The patient was a 33 year old housewife transferred to Loyola University Medical Center on December 17, 1975 with chest pain shortness of breath, and increasing fatigability.

She had been well until three weeks earlier when she noted the sudden onset of sharp retrosternal chest pain while at rest. The pain was not pleuritic and lasted ten minutes. Four days later the pain recurred radiated to the back, and was associated with severe dyspnea. Later that day she was admitted to another hospital where digoxin furosemide and coumadin were given and her symptoms improved. There was no history of fever chills hemoptysis, pedal edema or paroxysmal nocturnal dyspnea. There had been no recent exposures to toxins or animals. There was no history of rheumatic fever or hypertension. She used oral contraceptives for an unknown period of time prior to 1972. She had noticed mild upper respiratory infection during the month prior to the onset of her illness. She had been hospitalized for a dilation and curettage and an anxiety reaction during the past year. She bore two children the younger of whom

was 10 years old. She had been taking desiccated thyroid for menometrorrhagia for 15 years. She smoked less than one pack of cigarettes per day and drank two beers daily. Her parents, siblings and offspring were all alive. One sister had been evaluated for an arrhythmia.

On examination she was a white female comfortable at rest. The blood pressure was 88/68, the pulse 100/minute, the respiratory rate 20/minute. Temperature was 37° C. Funduscopic examination was normal. The thyroid was not enlarged. The jugular venous pressure was estimated above 20 cm with prominent CV waves. The chest was clear. A diffuse cardiac apex was felt in the fifth left intercostal space at the anterior axillary line. There was a prominent left parasternal lift. The first sound (S<sub>1</sub>) was decreased. The second sound (S<sub>2</sub>) was closely split. Ventricular (S<sub>3</sub>) and atrial (S<sub>4</sub>) gallop sounds were heard at the apex and left lower sternal border. A musical grade 3/6 holosystolic murmur with no respiratory variation was heard at the left lower sternal border and a grade 3/6 holosystolic murmur of different quality was present at the apex with radiation to the left axilla. A pericardial friction rub was noted along the left sternal border. The abdomen was flat. The liver was enlarged had a 23 cm span and was pulsatile. The spleen could not be palpated. The extremities revealed no clubbing or edema. The rest of the examination was unremarkable.

Initial laboratory data showed WBC 11,300 with 52 neutrophils, 32 lymphocytes, 11 mono-

From the Departments of Medicine and Pathology, Loyola University Stritch School of Medicine, Maywood, Ill., and the Department of Medicine, Evanston Hospital, Evanston, Ill.

This study was supported in part by NIH Training Grant HL05971.

Received for publication Dec 8, 1976.

Reprint requests: Rimgaudas Nemickas, M.D., Section of Cardiology, Loyola University Stritch School of Medicine, 2160 South First Ave., Maywood, Ill. 60153.



Fig 1 Chest roentgenogram posteroanterior (a) and lateral (b) views

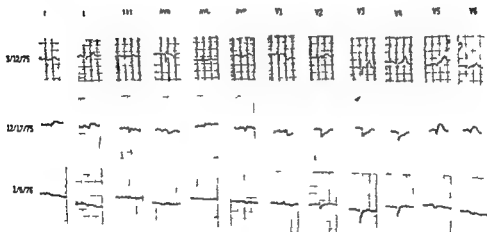


Fig 2 Electrocardiograms.

cytes 2 eosinophils and 3 basophils hemoglobin 13.8 Gm per cent and hematocrit 42 per cent Urinalysis was normal Serum sodium was 148 mEq/L potassium 4.3 mEq/L chloride 98 mEq/L  $\text{CO}_2$  content 28 mM/L and the venous pH was 7.43 The BUN was 26 mg per cent uric acid 10.6 mg per cent calcium 8.9 mg per cent phosphates 4.2 mg per cent glucose 140 mg per cent cholesterol 120 mg per cent total protein 7.2 Gm per cent albumin 3.9 Gm per cent and total bilirubin 0.7 mg per cent The alkaline phosphatase was 70 units LDH 340 units SGOT

65 units CPK 51 units (all MM isoenzyme) Thromboplastin time was 28.3 seconds and partial thromboplastin time was 48 seconds Initial ASO titer was 500 Todd units with 500 and 333 units on subsequent examinations Two throat cultures grew out normal flora Three blood cultures revealed no growth Stool examination for ova and parasites was negative T, resin uptake was 29 per cent T, M P was 70  $\mu\text{g}/100\text{ ml}$  and TSH was 2.7  $\mu\text{u}/\text{ml}$ .

DR ROCELIO MONCADA The chest roentgenogram on admission (Fig 1) showed marked

enlargement of the cardiac silhouette involving all four chambers. The pulmonary vasculature reflects increased pulmonary venous pressure, basilar vasoconstriction, and shifting of the pulmonary blood flow towards the upper lung fields. Interstitial edema was present in the lung bases. On subsequent films we failed to identify any signs of pericardial effusion.

DR JOHN F MORAN: A summary of selected tracings (Fig 2) from the normal tracing, prior to the onset of illness, through the last tracing showed the changes of an extensive anterolateral apical myocardial infarction, left axis deviation, complete right bundle branch block, and the progressive loss of QRS amplitude.

DR PATRICK J SCANLON: The echocardiogram showed a normal looking aorta and aortic valve and the left atrium was not grossly enlarged. Septal contraction was fairly normal, but the posterior wall contraction was increased. The diameter of the left ventricle was within normal limits. Mitral valve motion was good.

DR DAVID FISHMAN: The patient was continued on digoxin, furosemide, and coumadin. Prednisone 60 mg daily and erythromycin 250 mg four times daily were added. On the seventh hospital day a Swan Ganz catheter was inserted. The mean right atrial pressure was 25 mm Hg, pulmonary artery pressure was 38/20 mm Hg, and the mean pulmonary capillary wedge pressure was 28 mm Hg. On the eighth hospital day frequent premature ventricular contractions were treated with lidocaine. Nitroprusside infusion and fluid challenge did not affect the cardiac output on the ninth hospital day. On the twelfth hospital day the patient deteriorated and left cardiac catheterization with angiography was performed. On the thirteenth hospital day, Keflin was begun for a urinary tract infection. Additional laboratory data showed no change in acute and convalescent titers to the following organisms: Toxoplasma, Psittacosis, Adenovirus, Influenza A & B, Parainfluenza 1, 2 and 3, Eaton agent, Varicella, Zoster, and Cytomegalic virus. Fungal complement fixation studies were negative. The patient's condition worsened and an intra-aortic balloon pump was inserted. On the twentieth hospital day, cardiac catheterization was repeated to visualize the left ventricle in a different position and to obtain coronary arteriograms. On the twenty-first hospital day, the patient became

acidotic and thrombocytopenic. She died on the twenty-third hospital day.

### Clinical discussion

DR THOMAS KILLIP: When asked to give a cardiovascular CPC one often suspects that the patient has one of three things: a myxoma, IHSS, or a floppy mitral valve. I can confidently say that the patient had none of these. This is a most puzzling case, and I am not sure how much more I will be able to deduce.

Does the pain have any direct relation to the patient's heart problem? She had pain associated with severe dyspnea. There may be several reasons for this. One is if the pain is pleuritic and patient is unable to take a deep breath. We are told the pain was not pleuritic so that is not a factor. In massive pulmonary embolism there may be a sensation of dyspnea, presumably secondary to sudden and acute changes in lung compliance. Many patients with ischemic pain have dyspnea with the pain due to altered ventricular compliance and consequent increased left ventricular filling pressure. Presumably the dyspnea in this patient reflected acute heart failure which was treated when she was admitted to the other hospital 10 days before she was transferred here.

From physical examination we recognize that this young woman was severely ill. She was hypotensive. There were prominent CV waves in the jugular venous pulse which probably reflected significant tricuspid regurgitation. We are told that she had a parasternal lift. There are several causes for a parasternal lift. Systolic expansion of the left atrium from mitral regurgitation displaces the anterior structures forward. An overloaded dilated right ventricle is another cause as is aortic root movement in severe aortic regurgitation. A fourth cause that should not be overlooked is the possibility of a left ventricular aneurysm or a dyskinetic area expanding paradoxically during systole. We have enough information to suggest that she had mitral regurgitation and tricuspid regurgitation. One might wonder about the possibility of a ventricular septal defect, congenital or acquired, but I do not think the physical findings suggest this. She has an enormous liver and I presume this reflects congestion and tricuspid regurgitation. The laboratory values are not of any help at this point. I

am a little surprised that her liver function is not more abnormal. She has valvular dysfunction and severe myocardial dysfunction. We are not yet sure whether the valvular dysfunction is primary or secondary.

I agree with the interpretation of the electrocardiograms. It is significant that several months before she died she had a perfectly normal electrocardiogram. Then she developed striking abnormalities which can only be interpreted as an extensive loss of anterior forces and probably some strictly posterior ischemia. I am puzzled by the echocardiograms. I would have predicted we would see greater evidence of increased chamber size and reduction in contractility. The right heart pressures are significantly abnormal. Right atrial pressure is extraordinarily high, 25 mm Hg, about the same as the left atrial pressure. With such pressures one immediately thinks about the possibility of a constrictive or restrictive phenomenon. In the presence of normal chamber size, assuming the echo is correct, one must consider an infiltrative process involving the myocardium. Constrictive pericarditis characteristically demonstrates essentially equal filling pressures in both ventricles, a normal ejection fraction, usually normal contractility, and normal chamber sizes. Infiltrative processes simulate those hemodynamic findings. Further interpretation of the pressures will depend on what the left ventricular angiogram shows, the size of the chambers, and whether there are regional differences in contractility.

At this point we ask whether her illness is acquired or a congenital defect only recently manifested? A congenital problem seems unlikely. The possibility of an A-V fistula or anomalous coronary artery should be considered, but the patient had been through two normal pregnancies and had obviously seen physicians previously. When the left coronary artery arises from the pulmonary artery, in reality an A-V fistula, there is premature myocardial infarction and mitral regurgitation due to papillary muscle dysfunction. However, I believe the patient is too old for this diagnosis. If she truly has had a myocardial infarction as suggested by her electrocardiograms, an anomaly of the distribution of the coronary artery is a possibility. A massive infarction in a young person in whom there was a single left coronary and only a trivial right coronary

artery has been reported. Could this be an infectious process? A myocarditis with extensive damage? The Coxsackie virus is one of the more common causes of adult myocarditis but titers are not available to us.

How could a myocardial infarction have occurred? Was there a myocarditis or cardiomyopathy predisposing to the formation of a clot and a coronary embolus? Unrecognized bacterial endocarditis with coronary embolus seems unlikely. We have no history of drug ingestion but with the psychiatric history one wonders about the possibility of the phenothiazine toxicity. These drugs have been associated with striking electrocardiographic abnormalities and even with fatal myocardial infarction. Could she have a cardiomyopathy with a secondary myocardial infarction? This would be an unusual event. The most common form of cardiomyopathy recognized or unrecognized is alcoholic. One infectious disease, namely Chagas, is associated with electrocardiographic abnormalities and complete RBBB, but this lady is not from South America.

Could this be an infiltrative cardiomyopathy such as amyloid simulating a myocardial infarction? There is a peculiar condition termed Fiedler's myocarditis which should be considered. Fiedler's is an acute inflammatory process associated with myocardial degeneration and dysfunction, usually with eosinophilia. Friedberg has described a case in which the electrocardiogram simulated acute myocardial infarction but could not be demonstrated at autopsy.

From the evidence at hand we must conclude that this woman has lost a massive amount of anterior left ventricle and probably also the septum as it supports the tricuspid valve leading to a cardiomyopathy with or without aneurysm formation. The etiology is not clear. We may change our minds when we review the cardiac catheterization studies.

**DR DAVID FISHMAN:** The left ventricular end diastolic pressure was 25 mm Hg. The left ventriculogram showed an enlarged chamber with only the base and part of the inferior wall contracting. Moderate mitral regurgitation was present. Coronary arteries showed no gross obstructions.

**DR THOMAS KILLIP:** We now have a great deal of information. The question is what we can do with it. I cannot escape the supposition that this

patient has had a massive myocardial infarction. There are striking differences in contractility within the ventricle. There is a small ring of reasonably functioning myocardium at the base. But, why did this occur? Birth control pills are a possible cause of coronary thrombosis but she had been off them for several years. We do know, on an experimental basis, that myocardial infarction can be produced by injecting various substances which increase the platelet coagulability such as ADP, and that the platelet plugs can be found in the vessels from 10 minutes to a half hour after injection and that by two to three hours there is a diffuse myocardial infarction with no evidence of vascular obstruction. Coronary spasm has also been recognized and a few patients with myocardial infarction have had perfectly normal coronary arteries on angiography. Could this be a periarthritis or some sort of an inflammatory process? There is no evidence to suggest this. Unfortunately, I am unable to advance a specific etiology. I wonder about coronary spasm or some form of coagulation defect perhaps affecting the platelets which was evanescent but diffuse. Clearly the damage involved the vast majority of the left ventricle and left the patient with a form of cardiomyopathy. I cannot find evidence for a myocarditis or infiltrative disease. I believe the problem is myocardial infarction with extensive loss of left ventricular mass of uncertain cause.

### Autopsy findings

**DR GISSUR BRYNJOLFSSON:** The heart was quite large due to dilation of the left ventricle but weighed only 300 Gm. The epicardium was smooth and glistening and there were no adhesions between the pericardial sac and the epicardium. The coronary arteries were essentially normal (Fig 3). The myocardium of the anterior

and lateral wall of the left ventricle was extensively replaced by fibrous tissue and the wall markedly thinned in areas measuring only 2 to 3 mm in thickness (Fig 4). This myocardial lesion involved the apex and extended within 2.5 to 3 cm of the base of the left ventricle. Circumferentially, it measured up to 8 cm and extended from the septum to the posterior papillary muscle. The anterior papillary muscle appeared to be completely fibrotic. There was some focal fibrosis of the septum, at the base but otherwise the septum was of about normal thickness. A large portion of the posterior wall of the right ventricle was paper thin, measuring only about 1 mm in thickness.

The endocardium of the fibrotic portion of the left ventricle was thickened, white and opaque. There was a mural thrombus at the apex of the left ventricle measuring 1.5 cm in diameter. A small mural thrombus was also noted at the base of the right auricular appendage and two very small mural thrombi were noted in the superior vena cava. The valves were normal. There was moderate dilation of the mitral and tricuspid valve rings with the mitral measuring 11.5 cm and the tricuspid measuring 14 cm in circumference.

On microscopic examination there was marked lymphocytic infiltration of the myocardium, in part focal and in part diffuse (Fig 5) with extensive loss of myocardial cells in areas (myocytolysis) and some secondary fibrosis. In a large portion of the anterolateral wall of the left ventricle there was no remaining myocardium and the wall was made up of a thin layer of fibrous tissue and thickened endocardium (Fig 6). The same was true for a large portion of the posterior wall of the right ventricle where the wall in areas measured only about 1 mm in total thickness. In addition, there were scattered smaller areas where the myocardium had disap-

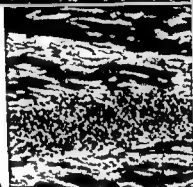
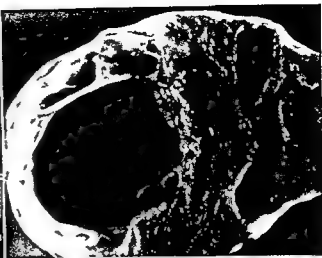
**Fig 3** The epicardium is smooth and glistening with no evidence of inflammatory reaction. The coronary arteries are normal.

**Fig 4** Cross-section of left and right ventricles. There is extensive replacement of the myocardium of the left ventricle by fibrous tissue. The wall is markedly thinned measuring in areas only 2 to 3 mm in thickness.

**Fig 5** A and B. Lymphocytic infiltration of the myocardium (A original magnification about  $\times 50$ , B original magnification about  $\times 600$ ).

**Fig 6** Cross section of the left ventricle. The myocardium has been entirely replaced by a thin layer of fibrous tissue. The inflammatory reaction has subsided. The endocardium is markedly thickened (Original magnification about  $\times 50$ ).

**Fig 7** Heavy lymphocytic infiltration at the junction of remaining myocardium and fibrous tissue (Original magnification about  $\times 50$ ).

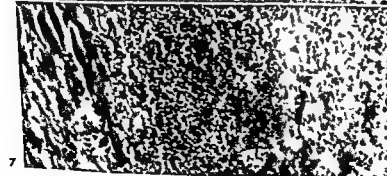


5A

5B



6



7

For legends see facing page

patient has had a massive myocardial infarction. There are striking differences in contractility within the ventricle. There is a small ring of reasonably functioning myocardium at the base. But, why did this occur? Birth control pills are a possible cause of coronary thrombosis, but she had been off them for several years. We do know, on an experimental basis, that myocardial infarction can be produced by injecting various substances which increase the platelet coagulability such as ADP, and that the platelet plugs can be found in the vessels from 10 minutes to a half hour after injection, and that by two to three hours there is a diffuse myocardial infarction with no evidence of vascular obstruction. Coronary spasm has also been recognized and a few patients with myocardial infarction have had perfectly normal coronary arteries on angiography. Could this be a periarthritis or some sort of an inflammatory process? There is no evidence to suggest this. Unfortunately, I am unable to advance a specific etiology. I wonder about coronary spasm or some form of coagulation defect perhaps affecting the platelets which was evanescent but diffuse. Clearly the damage involved the vast majority of the left ventricle and left the patient with a form of cardiomyopathy. I cannot find evidence for a myocarditis or infiltrative disease. I believe the problem is myocardial infarction with extensive loss of left ventricular mass of uncertain cause.

### Autopsy findings

**DR GISSUR BRYNJOLFSSON** The heart was quite large due to dilation of the left ventricle but weighed only 300 Gm. The epicardium was smooth and glistening and there were no adhesions between the pericardial sac and the epicardium. The coronary arteries were essentially normal (Fig 3). The myocardium of the anterior

and lateral wall of the left ventricle was extensively replaced by fibrous tissue and the wall markedly thinned, in areas measuring only 2 to 3 mm in thickness (Fig 4). This myocardial lesion involved the apex and extended within 2.5 to 3 cm of the base of the left ventricle. Circumferentially, it measured up to 8 cm and extended from the septum to the posterior papillary muscle. The anterior papillary muscle appeared to be completely fibrotic. There was some focal fibrosis of the septum at the base, but otherwise the septum was of about normal thickness. A large portion of the posterior wall of the right ventricle was paper thin, measuring only about 1 mm in thickness.

The endocardium of the fibrotic portion of the left ventricle was thickened, white and opaque. There was a mural thrombus at the apex of the left ventricle measuring 1.5 cm in diameter. A small mural thrombus was also noted at the base of the right auricular appendage and two very small mural thrombi were noted in the superior vena cava. The valves were normal. There was moderate dilation of the mitral and tricuspid valve rings with the mitral measuring 11.5 cm and the tricuspid measuring 14 cm in circumference.

On microscopic examination there was marked lymphocytic infiltration of the myocardium, in part focal and in part diffuse (Fig 5) with extensive loss of myocardial cells in areas (myocytolysis) and some secondary fibrosis. In a large portion of the anterolateral wall of the left ventricle there was no remaining myocardium and the wall was made up of a thin layer of fibrous tissue and thickened endocardium (Fig 6). The same was true for a large portion of the posterior wall of the right ventricle where the wall in areas measured only about 1 mm in total thickness. In addition there were scattered smaller areas where the myocardium had disap-

**Fig 3** The epicardium is smooth and glistening with no evidence of inflammatory reaction. The coronary arteries are normal.

**Fig 4** Cross section of left and right ventricles. There is extensive replacement of the myocardium of the left ventricle by fibrous tissue. The wall is markedly thinned, measuring in areas only 2 to 3 mm in thickness.

**Fig 5 A and B** Lymphocytic infiltration of the myocardium. (A: original magnification about  $\times 50$ ; B: original magnification about  $\times 500$ .)

**Fig 6** Cross section of the left ventricle. The myocardium has been entirely replaced by a thin layer of fibrous tissue. The inflammatory reaction has subsided. The endocardium is markedly thickened. (Original magnification about  $\times 50$ .)

**Fig 7** Heavy lymphocytic infiltration at the junction of remaining myocardium and fibrous tissue. (Original magnification about  $\times 50$ .)

appeared. The inflammatory reaction and myocytolysis involved all chambers of the heart and extends into the superior vena cava. The cell infiltrate was often heavy at the advancing edge of the lesions, i.e., at the junction between the areas of myocytolysis and the remaining myocardium (Fig. 7). In the older fibrotic areas most of the lymphocytes had disappeared. In one of the sections from the right ventricle two multinucleated giant cells were seen. There were a few small foci of recent hemorrhage and focal hemosiderin deposits. There were no primary vascular changes.

The endocardium, especially of the left ventricle, was markedly thickened due to proliferation of modified smooth muscle cells separated by mucoid material which on colloidal iron staining gave a deep blue color. There was also moderate increase in elastic tissue in the endocardium. The mural thrombus of the apex of the left ventricle showed considerable organization. The mural thrombus of the right atrium and superior vena cava showed early organization. Sections of the SA node revealed focal lymphocytic infiltration with loss of some nodal cells and secondary fibrosis. Other findings included chronic passive congestion of the lungs and the liver, moderate generalized edema, moderate hydrothorax, bilateral and ascites, bronchopneumonia, and marked fibrosis and atrophy of the thyroid with the gland weighing only 4.2 Gm.

The histologic findings in this case indicate that the myocardium was being destroyed by the lymphocytes (killer cells). It is considered likely that this patient had a viral myocarditis, although no virus was found on electron microscopy and then developed a delayed hypersensitivity reaction with myocytolysis brought about by the lymphocytes. The reactive fibrosis appears to be a great deal less than in healing infarction.

DR THOMAS KILLIP: Did you look at the skeletal muscle?

DR GISSUR BRYNJOLFSSON: Yes, it was normal.

DR THOMAS KILLIP: Do you have any speculation as to why the free wall of the left ventricle was primarily involved, extending into the septum? One would have thought that an inflammatory process would diffusely involve the entire myocardium.

DR GISSUR BRYNJOLFSSON: Yes, it did involve the entire myocardium but was not grossly visible throughout. Every section from the left ventricle and the septum where it looked grossly normal showed lymphocytic infiltration. The same was true of the right ventricle and both atria.

DR ROBERT CROKE: Do you suppose there is any connection between the thyroid and the myocardium?

DR GISSUR BRYNJOLFSSON: I do not think so. I think that the thyroid lesion was there for a long time. We quite often see thyroids like this.

### Comments

DR JOHN ROBINSON: I think this is a rather impressive example of the extreme lymphocyte cytotoxicity. It is beneficial when directed towards a tumor. It is unfortunate when it is directed towards the myocardium. These infiltrating lymphocytes indicate they are there for an immunologic reason. There must be new or changed antigens in the myocardium. Since there is no reason to think she had primary antigenic alteration of muscle structure, it is probably viral induced. Multiple auto antibodies including myocardial were looked for but none were found.

In response to Dr Killip's query about skeletal muscle pathology, patients with polymyositis have involvement of skeletal muscle but not ventricular muscle. The lymphocytes from these patients when incubated *in vitro* with normal myoblasts can destroy muscle cells within 4 hours. You actually do not even need the lymphocytes there. You can just simply take the supernatants from stimulated lymphocytes and rapidly kill muscle cells *in vitro*. So I think we can envision the pathogenesis of this patient's rapid cell loss and electrical changes occurring in ventricular muscle but we certainly do not have any specific etiology.

DR THOMAS KILLIP: Dr Gunnar, what was your clinical diagnosis when the patient died?

DR ROLF M. GUNNAR: We thought she had a viral myocarditis.

DR THOMAS KILLIP: Did you feel the electrocardiograms were compatible with that?

DR ROLF M. GUNNAR: We have seen patients with cardiomyopathy with electrocardiographic evidence of myocardial infarction.

DR HENRY LOEB: We have had some experi-





peared. The inflammatory reaction and myocytolysis involved all chambers of the heart and extends into the superior vena cava. The cell infiltrate was often heavy at the advancing edge of the lesions, i.e. at the junction between the areas of myocytolysis and the remaining myocardium (Fig 7). In the older fibrotic areas most of the lymphocytes had disappeared. In one of the sections from the right ventricle two multinucleated giant cells were seen. There were a few small foci of recent hemorrhage and focal hemosiderin deposits. There were no primary vascular changes.

The endocardium, especially of the left ventricle, was markedly thickened due to proliferation of modified smooth muscle cells separated by mucoid material which on colloidal iron staining gave a deep blue color. There was also moderate increase in elastic tissue in the endocardium. The mural thrombus of the apex of the left ventricle showed considerable organization. The mural thrombi of the right atrium and superior vena cava showed early organization. Sections of the SA node revealed focal lymphocytic infiltration with loss of some nodal cells and secondary fibrosis. Other findings included chronic passive congestion of the lungs and the liver, moderate generalized edema, moderate hydrothorax, bilateral and ascites, bronchopneumonia, and marked fibrosis and atrophy of the thyroid with the gland weighing only 4.2 Gm.

The histologic findings in this case indicate that the myocardium was being destroyed by the lymphocytes (killer cells). It is considered likely that this patient had a viral myocarditis, although no virus was found on electron microscopy, and then developed a delayed hypersensitivity reaction with myocytolysis brought about by the lymphocytes. The reactive fibrosis appears to be a great deal less than in healing infarction.

DR THOMAS KILLIP: Did you look at the skeletal muscle?

DR GISSUR BRYNJOLFSSON: Yes, it was normal.

DR THOMAS KILLIP: Do you have any speculation as to why the free wall of the left ventricle was primarily involved, extending into the septum? One would have thought that an inflammatory process would diffusely involve the entire myocardium.

DR GISSUR BRYNJOLFSSON: Yes, it did involve the entire myocardium but was not grossly visible throughout. Every section from the left ventricle and the septum where it looked grossly normal showed lymphocytic infiltration. The same was true of the right ventricle and both atria.

DR ROBERT CROKE: Do you suppose there is any connection between the thyroid and the myocardium?

DR GISSUR BRYNJOLFSSON: I do not think so. I think that the thyroid lesion was there for a long time. We quite often see thyroids like this.

### Comments

DR JOHN ROBINSON: I think this is a rather impressive example of the extreme lymphocyte cytotoxicity. It is beneficial when directed towards a tumor. It is unfortunate when it is directed towards the myocardium. These infiltrating lymphocytes indicate they are there for an immunologic reason. There must be new or changed antigens in the myocardium. Since there is no reason to think she had primary antigenic alteration of muscle structure, it is probably viral induced. Multiple auto antibodies including myocardial were looked for but none were found.

In response to Dr Killip's query about skeletal muscle pathology, patients with polymyositis have involvement of skeletal muscle but not ventricular muscle. The lymphocytes from these patients when incubated in vitro with normal myoblasts can destroy muscle cells within 4 hours. You actually do not even need the lymphocytes there. You can just simply take the supernatants from stimulated lymphocytes and rapidly kill muscle cells in vitro. So I think we can envision the pathogenesis of this patient's rapid cell loss and electrical changes occurring in ventricular muscle but we certainly do not have any specific etiology.

DR THOMAS KILLIP: Dr Gunnar, what was your clinical diagnosis when the patient died?

DR ROLF M. GUNNAR: We thought she had a viral myocarditis.

DR THOMAS KILLIP: Did you feel the electrocardiograms were compatible with that?

DR ROLF M. GUNNAR: We have seen patients with cardiomyopathy with electrocardiographic evidence of myocardial infarction.

DR HENRY LOEB: We have had some experi-

ence with endomyocardial biopsy, and the technique seems simple and safe. I wonder if in this patient a transvenous myocardial biopsy might have given indication of something more than just myocarditis in view of the massive accumulation of lymphocytes.

DR GISSUR BRYNJOLFSSON It is very possible we would have seen lymphocytic infiltration, it was that diffuse.

DR ROLF M GUNNAR I think it is a very important point in some of these desperately ill people. Because if we had seen her early and made the correct diagnosis, one wonders what effect large doses of steroids or other immunologically active agents would have had on this process.

DR JOHN ROBINSON Actually, we did consider immunosuppressive therapy in this patient. But in this patient with marked fibrosis, it would have been fruitless. The important point here is that if

you could detect lymphocytic infiltration earlier, you definitely would be justified in trying to turn off that response. Immediate treatment possibly with steroids, but for long term effects. I think you would have to consider azathioprine or cyclophosphamide to prevent lymphocyte cytotoxic responses. Antilymphocytic serum may be of value.

DR THOMAS KILLIP Well I want to congratulate Dr Brynjolfsson. I have never seen a case like this. It was extraordinary and obviously he put a great deal of work into the study of the case. One desperately wants to know the why of this process. We have a little bit of the how. If you find any more cases let us know. I hope you do not see any more, because I think this is the most frightening process I have been presented with in a long time.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., P.O. Box 765, Schenectady, N.Y. 12301, 518 374 4430 for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works, or for resale.

## Contemporary medical management of stable angina pectoris

R. Dirk Sostman M.D.

Rene A. Langou M.D.

New Haven, Conn.

This review will discuss approaches currently available in the United States for the treatment of "stable" angina pectoris due to atherosclerotic coronary artery disease. These include modification of life style, treatment of associated diseases, various nitrate compounds, the beta adrenergic blocking agent propranolol, and physical conditioning programs.

In the interest of clarity, more poorly understood forms of angina such as angina with angiographically normal coronary arteries<sup>1</sup> and a variant or Prinzmetal's angina<sup>2</sup> will not be discussed. Space limitations preclude consideration of unusual and as yet unproven therapeutic agents such as perhexiline, verapamil,<sup>3</sup> and dipyridylantoin<sup>4</sup> or of beta receptor blocking drugs not available in the United States. The latter subject is reviewed in detail by Prichard.

Understanding the physiology of and circulatory responses to anginal pain is essential to the rational management of coronary artery disease. Hence these topics will be discussed briefly. Additionally, some of the problems inherent in assessment of response to treatment will be mentioned since they are important both to practical clinical management of individuals with angina and to evaluation of therapeutic modalities.

### Physiology of angina pectoris

It is generally accepted that the primary pathophysiologic process causing anginal pain is the

inability of diseased coronary arteries to provide adequate blood flow to meet the oxygen requirements of the myocardium at a particular time. The determinants of this imbalance between supply and demand are complex.

While coronary artery stenosis is the sine qua non of typical angina,<sup>1-3</sup> it is not sufficient to explain the development of anginal pain.<sup>1,11</sup> Other factors which may contribute to reduced oxygen delivery to the myocardium include coronary-artery spasm or vasoconstriction<sup>12,13</sup> and abnormal blood oxygen transport.<sup>14</sup> The medical approach to increasing oxygen delivery to the myocardium has been based upon the use of vasodilator drugs which while successful in increasing myocardial blood flow in normal hearts have been uniformly ineffective in diseased coronary circulations.<sup>22,23</sup> At the present time attempts to increase total oxygen transport to the myocardium are within the province of surgical therapy.

Reduction of myocardial oxygen demand is the cornerstone of current medical therapy of angina. The total oxygen consumption of the heart depends upon several factors of differing importance.<sup>24,25</sup> Of lesser quantitative importance are the basal metabolism of the myocardium, external contractile element work, and the activation energy required for depolarization and electromechanical coupling. The major determinants of myocardial oxygen consumption (MVO<sub>2</sub>) are the systolic wall tension, the relative amount of time during which systolic wall tension is exerted, and the inotropic state of the heart. The ventricular systolic wall tension (T) is a function of ventricular dimensions (directly proportional to radius (r) and inversely proportional to thickness (h)) and developed pressure (P) so that

From the Department of Internal Medicine, Cardiology Section, Yale University School of Medicine, New Haven, Conn.

Received for publication April 18, 1977.

Reprint requests to: Rene A. Langou, M.D., Cardiology Section, Yale University School of Medicine, 333 Cedar Street, 87 LMP, New Haven, Conn. 06510.

$T = Pr/2h$ , the Laplace relationship for a spherical chamber. From this expression the oxygen costs of cardiac dilatation and systemic (and therefore intraventricular) hypertension may be appreciated. The time during which systolic wall tension is exerted is governed by the heart rate (the frequency with which tension must be developed) and probably the ejection time (the fraction of each cardiac cycle during which tension must be maintained). The heart rate, of course, also influences myocardial perfusion by changing the duration of diastole, contractility,<sup>28</sup> and probably the distribution of coronary blood flow.<sup>29, 30</sup> The product of tension and heart rate expresses the internal contractile element work of the heart. This and the contractility of the ventricle are the chief determinants of MVO<sub>2</sub>. The effect of inotropic stimuli on MVO<sub>2</sub> was appreciated from studies of the effects of sympathetic nerve stimulation<sup>31</sup> and catecholamine administration,<sup>3</sup> and has been shown in an isolated left ventricle preparation to have about the same influence on MVO<sub>2</sub> as systolic wall tension.<sup>32</sup> This explains the clinical observation that digitalis preparations may reduce the frequency or severity of anginal attacks when administered to patients with heart failure and ventricular dilatation: the decrease in developed tension more than offsets the increase in MVO<sub>2</sub> due to the inotropic effect of the glycoside.<sup>33</sup>

The precipitation of an anginal attack must involve the factors outlined above. The sequence of changes may be variable depending upon the patient's baseline state: psychologic factors<sup>34</sup> and the stress exerted upon him, but certain relatively constant hemodynamic changes have been described in the experimental settings of exercise and atrial pacing.<sup>35, 36, 37</sup> Myocardial ischemia results in a state of abnormal ventricular function characterized by increased left ventricular end diastolic pressure (LVEDP). This has been interpreted as acute reversible heart failure<sup>38</sup> or as decreased diastolic compliance.<sup>39</sup> Abnormal elevations of LVEDP are associated with shifts of the ventricular function curve downward and to the right; stroke volume and work are subnormal.<sup>40</sup> Consequently ventricular wall tension increases further increasing MVO<sub>2</sub><sup>41</sup> and reducing subendocardial blood flow.<sup>42</sup> Peripheral vasoconstriction manifested by increased systemic arterial pressure occurs<sup>43</sup> increasing afterload and thus ventricular wall tension. Regional wall motion abnormalities might conceivably result in in-

creases in contractility in unaffected regions of the myocardium.<sup>44</sup> These changes precede and accompany the development of pain. The pain itself and reflex sympathetic outpouring may accentuate contractility and afterload further increasing MVO<sub>2</sub>. Reflex coronary artery vasoconstriction on a neurogenic basis<sup>45</sup> might result in decreased oxygen supply to the heart as a result of anginal pain. The hemodynamic changes are reversed by termination of exercise and the accompanying decrease in venous return, adrenergic output and their concomitants. That the hemodynamic changes can be prevented or reversed, forms the basis of medical therapy.

### Basis for medical therapy of angina

The roles of smoking, diet, and style of life in the prevention of coronary artery disease are controversial in varying degrees,<sup>46, 47</sup> but most physicians agree that they are important areas for intervention in managing patients with angina.

Smoking cigarettes can be an important precipitating factor in angina pectoris. There are two main reasons for this. Systemically absorbed nicotine increases heart rate and both systolic and diastolic arterial pressure.<sup>48, 49</sup> Absorbed carbon monoxide decreases blood oxygen content and depresses left ventricular function. It is evident that these changes decrease the patient's hemodynamic reserve and make him liable to angina from lesser stresses and at lower levels of cardiac work. In some patients smoking a cigarette may itself be sufficient to precipitate an anginal attack. Although this view is not universally accepted,<sup>50</sup> we have found that cessation of smoking is symptomatically beneficial to most anginal patients. Achieving patient compliance is obviously not easy. The physician must take a serious approach and spend sufficient time discussing smoking with the patient. A good physician-patient relationship is more essential in this (and in other attempts to modify habitual behavior) than in any other aspect of the treatment of anginal patients. Judicious use of minor tranquilizers may be of slight benefit.

We place less importance on management of the patient's diet than on cessation of smoking. Weight reduction would appear to be psychologically helpful and to reduce systemic and thus cardiac work, but this is not definitively established.<sup>50</sup> Diet or (if necessary) drug-induced lowering of blood lipids is probably helpful.<sup>51, 52</sup> In our experience patients generally accept such a

prescription well. The current large selection of palatable foods containing polyunsaturated fats (and the national advertising campaigns mounted by some food manufacturers) are helpful to the physician's efforts. In case the physician feels cast in the role of denier of life's pleasures, it should be noted that there is no demonstrable relation between coronary artery disease and ethanol consumption.<sup>22</sup>

The subject of life style is somewhat more diffuse. Specifically, heavy meals and exertion in very hot, cold, or windy weather should be proscribed.<sup>1</sup> Beyond this, Aronow's statement that the patient should be guided away from stress<sup>4</sup> is succinct and about as specific as is usefully possible. If at all possible, we do not recommend that a patient cease pleasurable activities because they are associated with angina, one of the important rationales for drug therapy is to help preserve the quality of life. It may be helpful for the patient to work shorter, more regular hours, take more frequent vacations, and have regular exercise and recreation. The physician should, if possible, take an active role in helping the patient with emotional problems resulting from or contributing to his angina. Given the usual time constraints of medical practice, this often has less than satisfactory results. We have found minor tranquilizers beneficial in some cases; formal psychotherapy may, some times, be indicated. A helpful—indeed, essential—but sometimes neglected measure is discussion with the patient's family of his need for reassurance and a less stressful life style.

It is essential that associated conditions which predispose the patient to angina should be vigorously treated. Chronic pulmonary disease which hampers blood oxygenation should be treated in the most aggressive manner possible, of course, theophylline compounds and beta adrenergic agonists are clinically often found to exacerbate angina. Conversely, beta adrenergic-blockers which are not cardioselective, usually are of limited use in the anginal patient with obstructive pulmonary disease in which there is a significant bronchospastic component. Control of systemic arterial hypertension may be of significant benefit, presumably by reducing the systolic wall tension which the ventricle must develop. Treatment of congestive heart failure and particularly cardiac dilatation with digitalis and diuretics may decrease MVO and reduce the potential for angina. Digitalis may

have an additional role in medical treatment of angina in combination with the cardiodepressant beta blocking drugs in patients with abnormal ventricular function.<sup>23</sup> Exercise limitation due to failure can often be avoided,<sup>24</sup> presumably by retaining the negative chronotropic action of the beta blocker while countering its negative inotropic effect.<sup>25</sup> Digitalis may also be useful in patients with nocturnal angina, one cause of which is probably acute congestive failure due to fluid shifts into the pulmonary circulation and mobilization of edema fluid.<sup>21</sup> Anemia and hemoglobin abnormalities can impair oxygen delivery and should be reversed if possible. Drugs taken for other medical illnesses which directly or indirectly affect the heart, such as thyroid and steroid hormones, sympathomimetic and anorectic agents should be reviewed and, if possible, discontinued. Premature ventricular beats as well as both brady and tachyarrhythmias have been associated with increases in angina and appropriate treatment with drugs or an artificial pacemaker may significantly alleviate angina.<sup>2</sup> Hypothyroidism, which increases systemic and myocardial oxygen demands and hypothyroidism which may accelerate atherogenesis, should be identified and treated. Initiation of thyroid replacement should be done carefully, consultation with an endocrinologist is often helpful.

Reduction of myocardial oxygen demands at a particular level of activity and thus promotion of greater activity or less frequent pains can be achieved theoretically in several ways. Reduction of heart rate, decrease in inotropic state of the ventricle, and reduction in ventricular filling pressures are the major points of attack. Other factors which may alleviate angina at least partially through the above mechanisms are promotion of a psychologic sense of health, decreasing the circulatory demands of exercise, reduction in adrenergic drive, promotion of collateral vessel formation, and redistribution of regional myocardial blood flow.

### Nitrates

The first line pharmacologic agent in the treatment of angina is nitroglycerin. During the past several years, other nitrate esters have found extensive use in management of patients with coronary artery disease and oral and cutaneous administration have become popular. There is still some uncertainty concerning the modes of action of nitrates and the efficacy of long

acting compounds in various formulations and routes of administration is a matter of considerable controversy

The basic action of nitrates is vascular smooth muscle relaxation.<sup>37</sup> As they are currently used, the effects on other smooth muscle is not clinically significant

The mechanisms by which nitrates relax vascular smooth muscle is poorly understood but they may act through cyclic AMP.<sup>37</sup> There is a differential effect, with greater relaxation of venous smooth muscle, dilation of postcapillary resistance vessels and capacitance vessels, and significant venous pooling of blood.<sup>38-41</sup> There is a modest precapillary resistance vessel dilation,<sup>37-40-42</sup> although one study<sup>43</sup> found no change in total systemic vascular resistance. Systemic arterial systolic and mean pressures are lowered through arteriolar dilation and reduction in preload (and thus stroke volume).<sup>40-43</sup> Lowered arterial pressure causes a reflex increase in heart rate and contractility.<sup>43-45</sup> There is also a direct effect on contractility.<sup>4</sup> The peripheral venous pooling results in decreases in LVEDP<sup>40-43-46</sup> and left ventricular end diastolic volume<sup>40-42-47</sup> and in pulmonary artery pressure.<sup>45</sup> Left ventricular ejection rate<sup>40-47</sup> and  $dp/dt$ <sup>45</sup> are increased.

The rationale for the use of nitrates in angina is clear from the hemodynamic changes listed above. The decreases in venous return, ventricular filling pressure, and ventricular dimensions reduce wall tension, as does afterload reduction. Increased ejection rate and decreased ejection time due to afterload reduction and augmented inotropic state probably also reduce MVO. The tendency toward increased MVO, due to increases in heart rate and contractility is apparently offset by the beneficial hemodynamic changes induced by the drug.

The nitrate induced hemodynamic alterations are probably sufficient to explain the clinical results obtained with nitrates, effects on the coronary circulation itself are disputed. It is known that an index of MVO, the triple product of heart rate, systolic pressure and ejection time at onset of angina is unchanged by nitrates.<sup>37-44-47</sup> This suggests that nitrates lower MVO, at a given level of body work and do not increase oxygen delivery to the myocardium. Although it has been stated that nitrates cause coronary vasodilation,<sup>48-49</sup> intracoronary arterial administration of nitroglycerin fails to alleviate angina induced by pacing<sup>50</sup> while sublingual nitroglycerin reduces

MVO, and relieves angina<sup>51</sup> by its peripheral circulatory effects. Studies of total,<sup>52-54</sup> regional,<sup>55-57</sup> and subendocardial<sup>58-60</sup> coronary blood flow have yielded contradictory results, although definite conclusions do not seem justified yet. Some authors state that, while leaving total myocardial blood flow unchanged nitroglycerin increases subendocardial blood flow in both normal and ischemic regions of the ventricle.<sup>61</sup> There is little work on the effects of other nitrates on the coronary circulation.

The prompt onset of action of sublingual nitroglycerin makes it uniquely suitable for therapy of acute ischemic pain,<sup>59</sup> but its transient effect renders it ineffective in the prophylaxis of angina. Four avenues to prolonged nitrate action have been pursued thus far: organic nitrate esters alleged to be intrinsically long acting using sublingually or orally, sustained-release oral nitroglycerin preparations, and topical nitroglycerin.

Studies of "long acting" nitrates have demonstrated effects persisting longer than the usual effect of sublingual nitroglycerin.<sup>62-64</sup> In many of these reports, use of non equipotent doses makes interpretation difficult.<sup>65-67</sup> and the substitution of hemodynamic effects for antianginal effects may lead to erroneous conclusions.<sup>68</sup> Other studies have failed to show any advantage of long acting nitrates<sup>69</sup> or have even shown them to be no more effective than placebo.<sup>70-72</sup> Nevertheless these drugs are widely used clinically, and are thought effective, since the usual dose in clinical use is greater than the equipotent dose of nitroglycerin,<sup>73</sup> a longer duration of action with some suitability for prophylactic use,<sup>74</sup> not surprising. Chewable<sup>75</sup> or oral<sup>76</sup> formulations can give longer lasting hemodynamic effects, their antianginal effects have not yet been evaluated conclusively although a recent ergometric study<sup>77</sup> suggests considerable benefit two hours after administration of oral isosorbide dinitrate.

The development of sustained-release preparations of the inherently short acting nitroglycerin has been surrounded by similar controversy.<sup>78</sup> Although there is ample data documenting their sustained physiologic effects,<sup>79-83</sup> and some data concerning effect on exercise tolerance<sup>84</sup> there is still no comprehensive evaluation of their use in treatment of angina. This is surprising since oral nitroglycerin offers great potential advantages.

Topical application of nitroglycerin as an ointment has been known for a long time<sup>85</sup> but only

recently has there been much interest in its use. Hemodynamic effects persisting for three to six hours have been reported,<sup>103,104</sup> and two studies<sup>105,107</sup> convincingly demonstrated improved exercise tolerance from one to three hours after administration. Nitroglycerin ointment is one of the nitrate formulations proven to have long lasting effects on angina. It has found extensive recent clinical use in patients with nocturnal angina and tentative proof of its efficacy lends inferential support to the use of sustained-release nitroglycerin.

Since there is no evidence for tachyphylaxis, cross tolerance or post withdrawal rebound phenomena<sup>108</sup> with therapeutic doses of any currently used nitrate preparation it appears that prophylactic nitrate therapy is not harmful. Nitrate induced hypotension can result in syncope and may be dangerous in patients with cerebrovascular disease but the hypotension is not greater than that caused by nitroglycerin itself although subject to the same cautions. For nocturnal use nitroglycerin ointment seems preferable on the basis of available data; its inconvenience often precludes its use for ambulatory patients during the daytime. The prophylactic nitrate preparation to use during the daytime remains a matter of personal preference and individual result; no currently available drug or formulation has yet been conclusively recognized as efficacious. Frequent administration of sublingual nitroglycerin is a less convenient if perhaps more effective alternative<sup>109</sup> but is is doubtful that satisfactory compliance with this regimen can be achieved.

If nitrates are used without propranolol the optimum dose can be selected by the effect on blood pressure and heart rate. The greatest attainable decrease in blood pressure which is not attended by symptoms of hypotension (especially during orthostasis), intolerable headache or increase in resting heart rate of greater than 10 to 15 beats per minute indicates optimum nitrate therapy. As Goldstein and Epstein<sup>110</sup> have pointed out headache should not be used as a therapeutic endpoint. We have not found that it is often a limiting factor in therapy provided analgesics are given initially and the patient is reassured that it will diminish. The other physiologic results of nitrate therapy may limit the use of nitrates however and it is in these patients or in those in whom optimal nitrate therapy fails to control angina that propranolol is most valuable.

## Propranolol

Propranolol is well absorbed after oral administration and peak levels in the blood occur 1 to 2 hours later.<sup>111</sup> It is eliminated by hepatic clearance<sup>112</sup> with a biologic half life of 2 to 4 hours after intravenous administration,<sup>113</sup> but a reduced clearance leads to a half life of 4 to 6 hours after chronic oral administration.<sup>114</sup> The clearance may be increased in patients with renal disease.<sup>115</sup> It is 90 to 96 per cent bound when measured in the plasma of normal subjects.<sup>116</sup> The bioavailability of the drug given orally is low. Most of the absorbed dose is cleared from portal blood in the first pass through the liver by a saturable mechanism; the availability of small oral doses of the drug is very low but that of larger doses is disproportionately greater.<sup>116</sup> The clinical implication of this is that initial small oral doses of the drug will serve mostly to saturate liver binding sites producing small systemic effects. During chronic oral administration hepatic tissue binding sites probably remain saturated throughout the conventional dosage interval.<sup>117,118</sup> Large inter individual variations in plasma drug levels have been observed in human subjects receiving equal doses<sup>119</sup>; the pharmacologic and clinical effects of the drug appear to correlate reasonably well with plasma levels,<sup>118</sup> although the degree of beta blockade may be a more meaningful index.<sup>120</sup>

The hemodynamic properties of beta blockers have been extensively reviewed by Gibson.<sup>120</sup> The heart rate is decreased in normal subjects<sup>1</sup> and in patients with ischemic<sup>121</sup> and other organic<sup>122</sup> heart disease at rest and during stress<sup>123</sup> and after nitroglycerin administration.<sup>124</sup> The reduction in heart rate is related to the plasma propranolol concentration<sup>125</sup> and the effects of beta blockade do not significantly differ in normal subjects and in patients with ischemic heart disease.<sup>126</sup> There is a decrease in cardiac output,<sup>127,128,129</sup> with no change in stroke volume<sup>1</sup> which parallels the lowering of heart rate<sup>130</sup> but is not prevented in normals or patients with heart disease by artificially holding heart rate constant.<sup>131,132</sup> Systolic ejection rate is lowered by propranolol.<sup>133</sup> The rate of rise of left ventricular pressure is reduced at rest and during exercise.<sup>134</sup> The left ventricular end-diastolic pressure is usually increased<sup>135,136</sup> but may even be reduced.<sup>137</sup> A change in ventricular compliance has been suggested as the mechanism for the latter observations in the case of practolol. End diastolic



acting compounds in various formulations and routes of administration is a matter of considerable controversy

The basic action of nitrates is vascular smooth muscle relaxation.<sup>37</sup> As they are currently used, the effects on other smooth muscle is not clinically significant

The mechanisms by which nitrates relax vascular smooth muscle is poorly understood, but they may act through cyclic AMP.<sup>37</sup> There is a differential effect, with greater relaxation of venous smooth muscle, dilation of postcapillary resistance vessels and capacitance vessels, and significant venous pooling of blood.<sup>38-41</sup> There is a modest precapillary resistance vessel dilation,<sup>37-40</sup> although one study<sup>40</sup> found no change in total systemic vascular resistance. Systemic arterial systolic and mean pressures are lowered through arteriolar dilation and reduction in preload (and thus stroke volume).<sup>40-43</sup> Lowered arterial pressure causes a reflex increase in heart rate and contractility.<sup>43-45</sup> There is also a direct effect on contractility.<sup>3</sup> The peripheral venous pooling results in decreases in LVEDP<sup>40-43</sup> and left ventricular end diastolic volume<sup>40-43</sup> and in pulmonary artery pressure.<sup>43</sup> Left ventricular ejection rate<sup>40-47</sup> and  $dp/dt$ <sup>43</sup> are increased.

The rationale for the use of nitrates in angina is clear from the hemodynamic changes listed above. The decreases in venous return, ventricular filling pressure, and ventricular dimensions reduce wall tension as does afterload reduction. Increased ejection rate and decreased ejection time due to afterload reduction and augmented inotropic state probably also reduce MVO. The tendency toward increased MVO, due to increases in heart rate and contractility is apparently offset by the beneficial hemodynamic changes induced by the drug.

The nitrate induced hemodynamic alterations are probably sufficient to explain the clinical results obtained with nitrates, effects on the coronary circulation itself are disputed. It is known that an index of MVO, the triple product of heart rate, systolic pressure and ejection time at onset of angina is unchanged by nitrates.<sup>37-41</sup> This suggests that nitrates lower MVO<sub>2</sub> at a given level of body work and do not increase oxygen delivery to the myocardium. Although it has been stated that nitrates cause coronary vasodilation,<sup>48-50</sup> intracoronary arterial administration of nitroglycerin fails to alleviate angina induced by pacing,<sup>50</sup> while sublingual nitroglycerin reduces

MVO, and relieves angina<sup>51</sup> by its peripheral circulatory effects. Studies of total,<sup>52-54</sup> regional,<sup>55-57</sup> and subendocardial<sup>58-60</sup> coronary blood flow have yielded contradictory results, although definite conclusions do not seem justified yet, some authors state that, while leaving total myocardial blood flow unchanged nitroglycerin increases subendocardial blood flow in both normal and ischemic regions of the ventricle.<sup>57</sup> There is little work on the effects of other nitrates on the coronary circulation.

The prompt onset of action of sublingual nitroglycerin makes it uniquely suitable for therapy of acute ischemic pain<sup>3</sup> but its transient effect renders it ineffective in the prophylaxis of angina. Four avenues to prolonged nitrate action have been pursued thus far: organic nitrate esters alleged to be intrinsically long acting used sublingually or orally, sustained-release oral nitroglycerin preparations, and topical nitroglycerin.

Studies of "long acting" nitrates have demonstrated effects persisting longer than the usual effect of sublingual nitroglycerin.<sup>60-66</sup> In many of these reports, use of non equipotent doses makes interpretation difficult,<sup>74-77</sup> and the substitution of hemodynamic effects for antianginal effects may lead to erroneous conclusions.<sup>78</sup> Other studies have failed to show any advantage of long acting nitrates<sup>79</sup> or have even shown them to be no more effective than placebo.<sup>80-82</sup> Nevertheless, these drugs are widely used clinically, and are thought effective, since the usual dose in clinical use is greater than the equipotent dose of nitroglycerin,<sup>74</sup> a longer duration of action with some suitability for prophylactic use is not surprising. Chewable<sup>83</sup> or oral<sup>84</sup> formulations can give longer lasting hemodynamic effects, their antianginal effects have not yet been evaluated conclusively, although a recent ergometric study<sup>85</sup> suggests considerable benefit two hours after administration of oral isosorbide dinitrate.

The development of sustained-release preparations of the inherently short acting nitroglycerin has been surrounded by similar controversy.<sup>81</sup> Although there is ample data documenting their sustained physiologic effects,<sup>86-89</sup> and some data concerning effect on exercise tolerance,<sup>90</sup> there is still no comprehensive evaluation of their use in treatment of angina. This is surprising, since oral nitroglycerin offers great potential advantages.

Topical application of nitroglycerin as an ointment has been known for a long time<sup>91</sup> but only

congestive heart failure. The myocardial depressant actions of propranolol can usually be managed with standard therapy<sup>11</sup> it is wise to consider digitals or diuretic therapy in patients with even minimal signs of heart failure<sup>12</sup>. Propranolol may be especially hazardous in patients with sinus node dysfunction<sup>13</sup>. Although it has been suggested that the occurrence of asthma may not require drug discontinuation<sup>14</sup>, asthma and obstructive lung disease are often worsened intolerably. Patients on high doses of propranolol often report muscular weakness and fatigue. Peripheral vascular disease may be accentuated by beta blockade<sup>15</sup> but reported cases are few. Most serious reactions can be avoided by careful patient selection.

Cessation of propranolol administration may pose special hazards of myocardial infarction or increased angina<sup>16,17</sup>. A true rebound syndrome is suggested by changes in pattern of angina and the occurrence of infarction but the mechanism is obscure. It is possible that the phenomenon represents progression of the disease or alterations in numbers of receptor sites; controlled studies have not been done. It is presently considered advisable to taper the drug over a few days if cessation of therapy is necessary<sup>18</sup>.

Reported drug interactions are few. Catecholamine depleting agents may potentiate the effects of propranolol<sup>19,20</sup>. Propranolol may interfere with circulatory compensation responses to anesthesia. Propranolol-induced bradycardia may be potentiated by digitals intoxication.

For most patients with angina propranolol represents a safe and remarkably effective mode of therapy. If patients are carefully evaluated and propranolol administration is begun cautiously few adverse reactions will occur. In higher risk patients the use of propranolol may still be worth consideration although monitoring of therapy assumes greater importance and adjunctive treatment with other agents may be necessary.

#### Nitrate and propranolol therapy

It has long been thought that nitrates and beta adrenergic receptor blocking agents would exert synergistic or additive effects on myocardial oxygen consumption by their opposing circulatory effects<sup>21-23</sup>. Measurements of exercise capacity<sup>24,25</sup> and hemodynamic parameters<sup>26</sup> and clinical experience support this view. The addition of propranolol to nitrate therapy has

**Table 1** Hemodynamic and other alterations usually induced by propranolol nitrates and combined therapy

| Parameter | Propranolol | Nitrates | Combined |
|-----------|-------------|----------|----------|
| HR        | ↓           | ↑        | ↑        |
| CO        | ↓           | 0        | ↑        |
| LVSP      | ↓           | ↑        | ↑        |
| SAP       | 0           | ↑        | ↑        |
| SER       | ↓           | ↑        | ↑        |
| LVEDP     | ↓           | ↑        | ↑        |
| LVV       | ↑           | ↑        | 0        |
| dp/dt     | ↓           | ↑        | ↑        |
| TTI       | ↓           | ↑        | ↑        |
| CVR       | ↑           | ↓        | ↓        |
| SAP       | ↓           | ↑        | ↑        |

↑ = increase ↓ = decrease 0 = small or variable effect. Abbreviations: HR = heart rate CO = cardiac output LVSP = left ventricular systolic pressure SAP = systemic arterial pressure SER = systolic ejection rate LVEDP = left ventricular end-diastolic pressure LVV = left ventricular volume dp/dt = rate of rise of systolic pressure TTI = tension time index at a given workload CVR = coronary vascular resistance SEP = subendocardial perfusion.

been suggested to improve life expectancy in an uncontrolled series<sup>27</sup>. Currently most anginal patients in our institution are treated with combined nitrate and propranolol therapy.

The rationale for combined therapy centers on the often opposing hemodynamic actions of the two classes of agent; each should cancel the actions of the other which tend to increase MVO while the beneficial actions should usually be additive. A cardiac catheterization study has proved this assumption to be correct both at rest and during exercise in patients with ischemic heart disease<sup>28</sup>. A summary of the hemodynamic effects of the two classes of drug and of their combination is shown in Table 1. Significantly propranolol prevents nitrate induced tachycardia and increased contractility but does not prevent the nitrate induced reduction in left ventricular end diastolic pressure and (probably) in ventricular volume. The reduction in systemic arterial pressure and tension-time index may be additive; no adverse alterations occur.

The effects of continued therapy on the coronary circulation must also be considered in this instance; only hypothesis is possible for there is no experimental data. It is of interest though that both propranolol and nitrates are thought to increase subendocardial blood flow. Both agents reduce systolic wall tension but have different effects on diastolic perfusion. Nitrates reduce diastolic wall tension by reducing ventricular size

volume usually increases.<sup>110</sup> Systemic arterial pressure is lowered at doses which lower cardiac output, at lower doses there may be a pressor effect, which has been attributed to blockade of beta adrenergic vasodilation.<sup>110</sup> There may be a reduction of plasma volume.<sup>111</sup> The MVO in man is decreased at rest<sup>112</sup> and during exercise.<sup>113</sup> Some of the hemodynamic changes persist after withdrawal of beta blockade.<sup>113</sup> A potentially deleterious effect is increased coronary vascular resistance.<sup>113, 121</sup> There is a consistent decrease in coronary blood flow,<sup>65, 118, 114</sup> which may be partially a result of the lessened oxygen requirements of the myocardium. Although it is usually thought that local factors achieve maximum vasodilation in ischemic myocardium, coronary artery vasoconstriction has been proposed as a contributing factor in angina<sup>115</sup> and in this light, removal of the adrenergic vasodilation must be viewed with some concern. A possibly beneficial effect of propranolol on the coronary circulation is increased perfusion of the subendocardium,<sup>116, 117</sup> the region most vulnerable to ischemia.<sup>118</sup> The drug also shifts the oxyhemoglobin dissociation curve to the right.<sup>119</sup> Propranolol also restores normal platelet aggregability in patients with angina,<sup>120</sup> an action which may interfere with the possible role of platelet aggregation in the pathogenesis of myocardial ischemia.<sup>119, 120</sup>

The rationale for use of propranolol in the treatment of angina pectoris is clear from examination of its pharmacologic properties. The drug decreases MVO by actions upon all of its major determinants. Systemic arterial pressure, a factor in the ventricular systolic wall tension, myocardial contractility, and heart rate are all significantly affected. Detrimental effects due to depression of cardiac performance, increase in ventricular volume and prolongation of ejection time do not seem to outweigh the drug's beneficial effects. In a review of 331 patients studied between 1965 and 1969 78 per cent responded favorably to propranolol therapy.<sup>121</sup> A subsequent review<sup>10</sup> and several recent clinical trials<sup>16, 109, 119, 121, 126</sup> document substantial clinical and objective exercise tolerance improvement. The consideration of propranolol therapy is accompanied by two major questions: the suitability of the patient and the proper dose. The conservative approach is to reserve propranolol for those patients who, after treatment of associated disorders and maximal nitrate therapy still find that angina significantly interferes with

their daily life. In our opinion, the patient's subjective report is the only relevant guide in this decision. In modern practice, most anginal patients are eventually treated with propranolol. Since the blood levels of propranolol obtained from equal oral doses vary greatly,<sup>101, 102</sup> the magnitude of the drug's effects depends upon the prevalent sympathetic tone<sup>11</sup> and since serious adverse reactions are possible,<sup>119</sup> initiation of therapy even by the oral route should be cautious. Fortunately, adverse effects usually occur early in therapy, unfortunately, they are not usually dose dependent and often occur with small initial doses.<sup>10, 117</sup> The usual practice in our institution is to begin therapy with 20 mg four times a day and to double the dose every few days until a therapeutic end point is reached; some cardiologists prefer to initiate therapy with a shorter dosage interval for the first few doses. The resting pulse rate is a convenient physiologic guide of drug effect, the usual end point is a resting pulse of 45 to 55 beats per minute. It has been suggested that the peak exercise heart rate is a superior measure of therapeutic effect and that spurious medical failures may result from reliance on the resting pulse rate as a measure of adequate beta blockade.<sup>11</sup> Other end points include nausea or diarrhea and relief of anginal symptoms. About 70 to 85 per cent of patients report a significant decrease in frequency of angina.<sup>10, 37, 121, 126</sup> and ergometric testing documents improvement in exercise tolerance in this group.<sup>10, 10, 110, 11, 125</sup> It is impossible to predict which patients will not respond. At maximal doses exercise tolerance may not improve,<sup>119</sup> and clinical improvement may seem negligible if the pretreatment anginal frequency is low.<sup>110</sup> The reported effective dose ranges from 80 mg per day,<sup>121, 141</sup> to more than 2,000 mg per day,<sup>10</sup> the majority of patients require 160 mg to 320 mg per day.

The adverse effects of propranolol are largely pharmacologic effects that arise predictably as a result of its pharmacologic actions. Life threatening bradycardia and shock or angina complete heart block, ventricular fibrillation and congestive heart failure have been reported.<sup>13, 128, 142, 143</sup> Serious but not life threatening reactions included hypotension,<sup>137, 142</sup> lesser degrees of heart block,<sup>128</sup> gastrointestinal<sup>113, 11</sup> and neurological<sup>114, 141</sup> disturbances. Hypoglycemia<sup>110, 127</sup> and sodium retention<sup>110, 125</sup> are probably not serious except in insulin dependent diabetic patients<sup>127</sup> and in individuals with severe

this situation evaluation of propranolol therapy should include measurement of peak exercise heart rate

There are a number of published exercise programs for conditioning of anginal patients<sup>160-163, 176</sup> The pertinent characteristics of these have been reviewed by Wolfson and Costin.<sup>17</sup> Patients should be preselected by a general medical evaluation and a stress test should be performed in order to exclude patients in whom vigorous exercise is likely to be hazardous to establish a baseline at which work load should begin and to establish a heart rate guideline to limit peak exercise It is usual for anginal patients to take nitrates before and if necessary during exercise Exercises should not take place after a meal A warming up period should precede maximal exercise and a cooling off period should follow it Supramaximal effort is deleterious The workload is increased at regular intervals Resuscitation equipment and personnel should be available at least for high risk patients

Marked improvements in exercise tolerance can usually be found within 6 weeks after beginning an exercise program Documentation of improvement by serial exercise testing provides psychological benefit to the patient and a contemporary guideline for the physician Exercise in the coronary patient should be thought of in the same way as drug therapy both should be continued indefinitely The risks of a properly conducted physical conditioning program are small minor orthopedic complaints which do not require specific therapy are the most common complication One poorly quantifiable but unique benefit of physical training is psychological most patients report a reduced fear of their disease an improved body image and a generally more positive attitude

#### Evaluation of therapy

Assessment of the results of therapy of angina is important both to practical clinical management of individual patients and to comparison of therapeutic modalities in the setting of a clinical trial The usual methods are evaluation of patient's subjective reports of the results of therapy statistical treatment of numerical parameters such as consumption of nitroglycerin tablets or frequency of anginal attacks<sup>12, 13, 16 and</sup> the standardized exercise test<sup>67, 12, 13, 16, 175</sup>

Subjective reports from the patient concerning the efficacy of therapy are the mainstay of clinical practice This approach is often disparaged as unscientific and prone to bias or placebo effect but, as Feinstein<sup>177, 178</sup> has pointed out the direct consequences of angina to the individual patient concern more than ergometry For this reason simple history taking is the most effective mode of evaluation of results of therapy in daily practice In the same setting the consumption of nitroglycerin may be a useful index if account is taken of external factors which may influence it Use of subjective or semi subjective parameters in clinical trials may complement ergometric data if questionnaires are thoughtfully designed<sup>179</sup> and if statistical treatment of results is appropriate<sup>180</sup> In this regard it is of interest that soft histonic and hard ergometric data usually agree<sup>1, 133, 136</sup>

The exercise test is an essential benchmark in clinical trials of antianginal therapies It provides a physiological basis for evaluation of therapy and a controlled situation which is invaluable for purposes of statistical treatment and inter institutional comparison It is important both for longitudinal assessment of individual patients and for clinical trials that the test be conducted with a progressive slowly-applied workload This method does not alter the endpoint of the test and permits greater sensitivity in detection of true but small differences<sup>17, 179</sup> High initial workloads may alter the endpoint of the test<sup>17</sup> The usefulness of exercise testing in clinical practice is not limited to diagnosis It provides a controlled situation selectively free from influence by the current events of the patient's life and may be useful in differentiating the effects of these from progression of disease It may be of help in deciding whether a patient may return to particular physical activities including a strenuous occupation The use of exercise testing in conjunction with physical conditioning programs has already been discussed Finally objective documentation of improvement is often of substantial psychological benefit to the patient

#### Medical failures

In certain situations it is unarguable that medical therapy of angina has failed for example the occurrence of myocardial infarction or continued clearly debilitating angina or progression of stable angina to the intermediate coronary

**Table II Hemodynamic changes during exercise before and after physical conditioning in anginal patients compared with propranolol nitrate therapy**

| Parameter | Untrained | Trained | Propranolol Nitrate |
|-----------|-----------|---------|---------------------|
| HR        | ↑ ↑       | ↑       | ↑                   |
| SAP       | ↑ ↑       | ↑       | ↑                   |
| CO        | ↑ ↑       | ↑       | ↑                   |
| dp/dt     | ↑ ↑       | ↑       | ↑                   |
| LVEDP     | ↑         | ↑       | ↑                   |

↑ = large increase ↓ = smaller increase HR = heart rate  
 SAP = systemic arterial pressure CO = cardiac output dp/dt = rate of rise of systolic pressure LVEDP = left ventricular end-diastolic pressure

and may increase the subendocardial perfusion pressure.<sup>37</sup> Propranolol increases subendocardial perfusion probably by increasing the duration of diastole. From inspection of these effects, one may conclude that there are no competing beneficial actions, and that propranolol and nitrates may have additive beneficial effects on subendocardial perfusion. For example the combination should both increase diastolic time and decrease diastolic wall tension. The effects of each class of agent on different components of coronary vascular resistance and the ultimate importance if these effects themselves are poorly understood. Here only speculation is possible.

The clinical use of combined propranolol and nitrate therapy does not significantly differ from the use of either alone except perhaps in its results. Nitrates do not usually prevent clinically significant propranolol induced congestive heart failure, nor do they affect the usefulness of the resting or exercising pulse rate as a guide to the degree of beta blockage. Propranolol might interfere with maximal nitrate therapy by reducing the tachycardic response to hypotension, but in our experience this is not often a problem. If it is we maintain the propranolol dosage at the expense of the nitrate regimen.

### Physical conditioning

Since physical conditioning improves exercise tolerance in normal subjects, it should not be surprising that it also does so in patients with ischemic heart disease,<sup>88, 160, 161</sup> although no improvement may occur if insufficient exercise is done to produce conditioning,<sup>165, 166</sup> and improperly performed exercise may be harmful.

The hemodynamic concomitants of exercise

before and after physical training in anginal patients are summarized in Table II. The effects of propranolol-nitrate therapy are included for comparison. Physical conditioning attenuates the effects of exercise—on heart rate, cardiac output, and myocardial contractility. As a result of this improved circulatory efficiency, the  $\dot{V}O_2$  (as determined from non invasive indices) at a given workload increases less in a trained subject permitting greater activity without the development of angina. The chronic effects of conditioning are approximately equal in antianginal potency to the acute effects of nitroglycerin.<sup>169</sup> Increased plasma fibrinolytic activity during exercise may retard the development of atheromata.<sup>170</sup> There may be a reduction in frequency of premature ventricular beats.<sup>167</sup> It is important to note that although reduction in cardiac death has been reported in normal persons and in patients with coronary heart disease<sup>168</sup> who engage in vigorous exercise, the statistical validity of most of these studies has been challenged.<sup>169</sup> Hence, the proven benefits of exercise training as all other current therapies for coronary artery disease except perhaps beta blockade,<sup>176, 177</sup> are limited to symptomatic improvement.

The beneficial effects of physical training are at least partially<sup>177</sup> due to alterations in peripheral hemodynamics. Greater oxygen extraction by skeletal muscle<sup>164</sup> probably due to alterations in oxidative enzyme activity<sup>173</sup> allows decreased blood flow at a given work load.<sup>173</sup> Probably as a consequence of this, plasma catecholamine levels during exercise are reduced in conditioned subjects.<sup>174</sup> No direct cardiac effects of conditioning have been conclusively documented in man, although animal experiments suggest increased collateral vessel formation.<sup>175</sup> Coronary blood flow and myocardial oxygen consumption during atrial pacing are not affected. Coronary arteriograms in man are unchanged.<sup>161</sup> It has been suggested<sup>162</sup> but not confirmed<sup>161</sup> that left ventricular performance is enhanced as a result of conditioning. Favorable alterations in regional myocardial blood flow to ischemic areas has been proposed<sup>178</sup> but not proven.

Clinical experience demonstrates that the effects of physical conditioning are additive to those of drugs. Another important interaction is that an effective drug treatment program may be necessary in order to permit patients to participate in a physical training regimen. Especially in

22. Charlier R. Antianginal Drugs. Berlin, 1971 Springer Verlag
23. Aronow W S The medical treatment of angina pectoris I Relationship of angina pectoris to coronary artery insufficiency *Am HEART J* 83 841 1972.
24. Sonnenblick P H, Ross J Jr., and Braunwald E. Oxygen consumption of the heart, *Am J Cardiol* 22 338 1968
25. Ross J S Pathophysiology of coronary circulation *Br Heart J* 33 173 1971
26. Braunwald E Control of myocardial oxygen consumption *Am J Cardiol* 27 416, 1971
27. Epstein S H Redwood D R, Goldstein R E et al. Angina pectoris pathophysiology evaluation and treatment *Ann. Intern. Med.* 75 53 1971
28. Boertin R C Couell, J W Pool, P E, et al. Increased myocardial oxygen consumption and contractile state associated with increased heart rate in dogs *Circ Res* 24 795 1969
29. Neill W A Phelps N C, Ozendine J M et al. Effect of heart rate on coronary blood flow distribution in dogs *Am J Cardiol* 32 306 1973
30. Buckberg B D Fixler D E, Archie J P, et al. Experimental subendocardial ischemia in dogs with normal coronary arteries *Circ Res* 30 67 1972.
31. Gregg D E Physiology of the coronary circulation *Circulation* 27 1128 1963
32. Krasnow N Rolett E L, Yurchak P et al. Isoproterenol and cardiovascular performance *Am J Med* 37 14 1964
33. Graham T P Jr., Couell J W Sonnenblick W H, et al. Control of myocardial oxygen consumption. Relative influence of contractile state and tension development *J Clin Invest* 47 315 1968
34. Couell J W Braunwald E Ross J Jr et al. Studies on digitalis XVI Effects on myocardial oxygen consumption *J Clin Invest* 45 1335 1966
35. Lane F M Mental mechanisms and the pain of angina pectoris *Am HEART J* 85 563 1973
36. Parker J O Hemodynamic and metabolic changes during myocardial ischemia *Arch Intern Med* 129 790 1972
37. Parati J W Pharmacological approaches to the therapy of angina *Adv Drug Res* 9 103 1974
38. Parker J O Ledwith J R West R O et al. Reversible cardiac failure during angina pectoris *Circulation* 39 745 1969
39. Wiener L Dwyer E M Jr and Cox J W Left ventricular hemodynamics in exercise induced angina pectoris *Circulation* 38 240 1968
40. Dwyer E M Jr Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing *Circulation* 42 1111 1970
41. Sharma B and Taylor S H Reversible left ventricular failure in angina pectoris *Lancet* 2 907 1970
42. Becker L and Pitt B Regional myocardial blood flow ischemia and antianginal drugs *Ann Clin Res* 3 33 1971
43. Roughgarden J W Circulatory changes associated with spontaneous angina pectoris *Am J Med* 41 347 1966.
44. Rose M Smoking and cardiovascular disease *Am HEART J* 85 836 1973
45. Seltzer C C Smoking and cardiovascular disease *Am HEART J* 80 125 1975
46. Boyer J L Coronary heart disease as a pediatric problem. Prevention through behavior modification *Am J Cardiol* 33 784 1974
47. Bonanno J A, and Lee J E Effects of physical training on coronary risk factors, *Am J Cardiol* 33 760 1974.
48. Aronow W S The medical treatment of angina pectoris IV. The medical management of angina pectoris *Am HEART J* 85 75 1973.
49. Aronow W S, Cassidy J, Wandrow J S, March H, Kern, J C, Goldsmith, J R, Kwetka M, Pagano J, and Lawter M Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients *Circulation* 50 340 1974
50. Sharma, B., Thadani, U., and Taylor S H Cardiovascular effects of weight reduction in obese patients with angina pectoris *Br Heart J* 38 504 1974
51. Baerenbaum M L To diet or not to diet and what diet? *Am HEART J* 87 401 1974
52. Barborak J J Rumm, A A, Anderson, A J., Schmid hoffer M and Tristani, F E Coronary artery occlusion and alcohol intake *Br Heart J* 39 289 1977
53. Lewis B L, Lubin R J, January L E, et al. *Rauwolfia serpentina* in the treatment of angina pectoris, *Circulation* 14 227 1956.
54. Georgopoulos, A J, Stone F M and Page I H Relationship between arterial pressure and exertional angina pectoris in hypertensive patients, *Circulation* 23 892, 1961
55. Crawford M H, Lewinter M M O'Rourke R A et al. Combined propranolol and digoxin therapy in angina pectoris *Ann. Intern. Med.* 83 449 1975
56. Duner H and Pernow B Hemodynamic effects of  $\beta$  receptor blocking agents and digitalis in ischemic heart disease with angina pectoris *Acta Med Scand* 194 517 1973
57. Harding P R Aronow W S and Eisenman J Digitalis as an antianginal agent *Chest* 64 479 1973
58. Goldstein R E and Epstein S E Medical management of patients with angina pectoris, *Progr Cardiovasc Dis* 14 360 1972
59. Mason D T and Braunwald E The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm *Circulation* 32 755 1965
60. Miller R R, Vismara L A, Williams, D O, et al. Pharmacologic mechanisms for left ventricular unloading in clinical congestive heart failure *Circ Res* 39 127 1976
61. Ablad B and Johnsson G Comparative effects of intra arterially administered hydralazine and sodium nitrite on blood flow and volume of forearm *Acta Pharmacol Toxicol.* 20 1 1963
62. Williams J F Glick G and Braunwald M Studies on cardiac dimensions in unanesthetized man effects of nitroglycerin *Circulation* 32 767 1967
63. Robinson F B Mode of action of nitroglycerin in angina pectoris *Br Heart J* 30 290 1968
64. Goldstein R E and Epstein S E Medical management of patients with angina pectoris, *Progr Cardiovasc Dis* 14 360 1972
65. Wiener L, Dwyer E M Jr and Cox J W Hemodynamic effects of nitroglycerin, propranolol, and their combination in coronary heart disease *Circulation* 39 623 1969
66. Lee S J K, Sung Y K, and Zaro A A J Effects of nitroglycerin on left ventricular volume and wall tension in patients with ischemic heart disease *Br Heart J* 32 390 1970
67. Goldstein R E Roseng D R Redwood, R et al. Clinical and circulatory effects of isosorbide dinitrate *Circulation* 43 629 1971
68. Geusmi, G Quantitative angiography the measure

syndrome. Often, however, failure of medical therapy is a highly subjective and individual judgment. A patient who desires to return to a job which demands heavy physical exertion may be unacceptably incapacitated at a functional level which many anginal patients do not even dream of achieving. Another patient in the same position may be able to assume a more sedentary occupation, and may be satisfied with therapy which allows him to resume doing odd jobs at home. Still other patients become cardiac neurotics and deny themselves activities which they are physiologically capable of undertaking.

In the broadest sense the goal of medical therapy of angina is to return the patient to a functional status which is satisfactory to him. Since no currently available treatment is clearly capable of prolonging the life span of patients with coronary artery disease, this consideration is, regrettably, irrelevant. The preconceptions of the physician concerning the patient's goals should be a lesser consideration.

In many instances medical failure is an indication for cardiac catheterization, and for coronary artery surgery if surgery holds reasonable promise of success. This is an appropriate consideration in debilitating or unstable angina or in the patient who desires to be free of angina and is willing to accept the risks of operative morbidity and mortality and of surgical failure.

When the indications for surgery are less clear, or when coronary angiography demonstrates surgically inoperable disease, the patient's status and current medical regimen should be meticulously reviewed. Weight reduction may be more attainable, or compliance with drug therapy increased, when there is no alternative. Exercise testing may reveal a disparity between resting and peak exercise heart rate which provides a rationale for more aggressive propranolol therapy. A carotid sinus nerve stimulator may be considered. In the case of the cardiac neurotic or the patient whose economic problems are paramount the help of a psychiatrist or a social worker may be invaluable. It is in this situation where the proper course of action is unclear and current therapy unsuccessful that the physician's medical skill and his ability to communicate with his patient are most severely taxed.

#### REFERENCES

1. Lukoff W, Segal B L and Kasparian H. Paradox of normal selective coronary arteriograms in patients

- considered to have unmistakable coronary heart disease. *N Engl J Med* 276:1063-1967
2. Dwyer E M Jr, Wiener L and Cox J W. Angina pectoris in patients with normal and abnormal coronary arteriograms: hemodynamic and clinical aspects. *Am J Cardiol* 23:639-1969
3. Kemp H G, Elliott W C and Gorlin R. The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 80:59-1967
4. Robinson J S. Prinzmetal's variant angina pectoris. *Am Heart J* 70:797-1965
5. Whiting R B, Klein M D, Vander veer J et al. Variant angina pectoris. *N Engl J Med* 282:709-1970
6. Silverman M M and Flamm M D. Variant angina pectoris: anatomic findings and prognostic implications. *Ann Intern Med* 75:339-1971
7. Pepine C J, Schang J J and Bemiller C H. Effects of perhexilene in symptomatic and hemodynamic responses to exercise in patients with angina pectoris. *Am J Cardiol* 33:806-1974
8. Andreasson F, Boye E, Christofferson E et al. Assessment of verapamil in the treatment of angina pectoris. *Eur J Cardiol* 2:443-1975
9. Taylor C R. Double blind crossover study of diphenhydantoin in angina pectoris. *Chest* 65:427-1974
10. Frichard B N C.  $\beta$  adrenergic receptor blocking drugs in angina pectoris. *Drugs* 7:55-1974
11. Prouditt W L, Shirey G K and Sones F M Jr. Selective cine coronary arteriography: correlation with clinical findings in 1000 patients. *Circulation* 33:901-1966
12. Ross R S and Friesinger G C. Coronary arteriography. *Am Heart J* 72:437-1966
13. Demany M S, Tambe A and Zimmerman H A. Correlation between coronary arteriography and the post exercise electrocardiogram. *Am J Cardiol* 19:526-1967
14. Blumgart H L, Schlesinger M J and Davis D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings. With particular reference to the significance of the collateral circulation. *Am Heart J* 19:1-1940
15. Allison R H, Rodriguez F L, Higgins E A et al. Clinicopathologic correlations in coronary atherosclerosis. Four hundred thirty patients studied with post mortem coronary angiography. *Circulation* 27:170-1963
16. Gilbert N C, Fenn G K and Leroy G V. The effects of distention of abdominal viscera on the coronary blood flow and on angina pectoris. *JAMA* 115:1962-1940
17. Nagalioni A, Finkelstein D and Bookus H L. Role of gastric distention in angina pectoris. *Am J Cardiol* 11:253-1963
18. Cheng T O, Bashour T, Singh B K et al. Myocardial infarction in the absence of coronary atherosclerosis. *Am J Cardiol* 30:680-1972
19. Mudge G H Jr, Grossman W, Mills R M Jr et al. Reflex coronary artery vasoconstriction in patients with ischemic heart disease. *N Engl J Med* 295:1333-1976
20. Eliot H S and Bratt G. The paradox of myocardial ischemia and necrosis in young women with normal coronary arteriograms. *Am J Cardiol* 23:633-1969
21. Regan T J, Timmis G, Gray M et al. Myocardial oxygen consumption during exercise in fasting and lipemic subjects. *J Clin Invest* 40:1624-1961

- propranolol I. Elimination during oral absorption in man. *Pharmacology* 7:33, 1972.
- 107 Evans G. H., and Shand D. G. The disposition of propranolol VI. Independent variation in steady state circulating drug concentrations and half-life as a result of plasma binding in man. *Clin. Pharm. Ther.* 14:434-440, 1971.
  - 108 Evans G. H., and Shand D. G. The disposition of propranolol V. Drug accumulation and steady state concentrations during chronic oral administration. *Clin. Pharmacol. Ther.* 14:457, 1972.
  - 109 Pine, M., Favre, L., Smith, S., McDonald, K., and Chisley L. A. Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. *Circulation* 52:866, 1975.
  - 110 Gibson, D. G. Pharmacodynamic properties of  $\beta$  adrenergic receptor blocking drugs in man. *Drugs* 1:2, 1974.
  - 111 Collier, D. J., and Shand, D. G. Plasma propranolol levels in the quantitative assessment  $\beta$ -adrenergic blockade in man. *Br Med J* 3:731, 1970.
  - 112 Jackson, G., Atkinson, L., and Oram, S. Reassessment of failed beta-blocker treatment in angina pectoris by peak-exercise heart rate measurements. *Br Med J* 3:616, 1975.
  - 113 Eliassch, H., Rosen, A., and Scott, W. M. Systemic circulation response to stress of simulated fight and to physical exercise before and after propranolol blockade. *Br Heart J* 29:617, 1967.
  - 114 Fitzgerald, J. D., Rowlands, D. J., Howitt, G., and Davies, P. T. L. Heart rate response to certain physiological maneuvers proposed measure of degree of beta adrenergic blockade (Abstr.) *Br Heart J* 33:614, 1971.
  - 115 Fröhlich, E. D., Tarazi, R. C., Dustan, H. P., and Page, I. H. The paradox of beta-adrenergic blockade in hypertension. *Circulation* 37:417, 1968.
  - 116 Bloomfield, H. A., and Sowton, E. A. Rate-independent effects of propranolol. The differentiation between chronotropic motropic and peripheral vascular responses. *Circ. Res.* 21:III 743, 1967.
  - 117 Donoso, E., Conn, L. J., Newman, B. J., Bloom, H. S., Stein, W. G., and Friedberg, C. K. Effects of propranolol on patients with complete heart block and implanted pacemakers. *Circulation* 36:534, 1967.
  - 118 Lewis, M. M., Brink, A. J., Theron, M. J., and Kotze, J. C. V.  $\beta$ -adrenergic blockade. Hemodynamics and myocardial energy metabolism in patients with ischemic heart disease. *Am J Cardiol* 21:846, 1968.
  - 119 Cunningham, G. R., and Carr, W. Hemodynamic response to exercise after  $\beta$ -adrenergic and parasympathetic blockade. *Can. J. Physiol. Pharmacol.* 45:813, 1967.
  - 120 Graber J., Khanna H. K., Raphael, M. J., Steiner R. E., and Webb-Peploe M. M. Effect of cardioselective beta adrenergic blockade in patients with abnormal left ventricular function (Abstr.) *Br Heart J* 33:615, 1971.
  - 121 Julius S. Pascual, A. V., Abbrevitt P. H., and London R. Effect of  $\beta$ -adrenergic blockade on plasma volume in human subjects. *Proc. Soc. Exp. Biol. Med.* 140:382, 1972.
  - 122 Tarazi, H. C., Fröhlich, E. D., and Dustan, H. P. Plasma volume changes with long term beta adrenergic blockade. *Am Heart J* 82:770, 1971.
  - 123 Wolfson S., Heuble R. A., Herman, M. V., Kemp H. G., Sullivan J. M., and Gorlin R. Propranolol and angina pectoris. *Am J Cardiol* 18:343, 1966.
  - 124 Wolfson, S. and Gorlin R. Cardiovascular pharmacology of propranolol in man. *Circulation* 40:911, 1969.
  - 125 Ertolin, T., Ebbat, O., and Lundman, T. Effects remaining after withdrawal of long term beta receptor blockade. *Br Heart J* 33:1065, 1974.
  - 126 Winbury, M. D., Wenz, H. R., and Howe B. E. Effects of  $\beta$ -adrenoceptor blockade and nitroglycerin on myocardial oxygenation. *Eur J Pharmacol.* 16:271, 1971.
  - 127 Moor T. W. Subendocardial distribution of coronary blood flow and the effect of antiaanginal drugs. *Circ. Res.* 30:621, 1972.
  - 128 Oak, F. A., Miller L. D., and Delivoria-Papadopoulos, M. Oxygen affinity in red cells changes induced in vivo by propranolol. *Science* 175:1372, 1972.
  - 129 Frishman, W. H., Weissler, B., Christodoulou, J. I., Smith, C., and Kilip, T. Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. *Circulation* 50:987, 1974.
  - 130 Borz, G. V. R. Platelet pharmacology in relation to thrombosis. *Adv. Cardiol.* 4:181, 1970.
  - 131 Harrison, D. C. Circulatory effects and clinical uses of beta-adrenergic blocking drugs. *Ann. Intern. Med.* 1972, Excerpta Medica Publishers, p. 7.
  - 132 Alderman, E. L., Davies, R. O., Crowley J. J., Lopez, V. G., Brooker J. Z., Friedman, J. P., Graham, P. F., Matol, N. J., and Harrison, D. C. Dose response effectiveness of propranolol for treatment of angina pectoris. *Circulation* 51:944, 1975.
  - 133 Jackson, G., Atkinson, L., and Oram, S. Double-blind comparison of tolamol, propranolol, pivalol and placebo in the treatment of angina pectoris. *Br Med J* 1:708, 1975.
  - 134 Miller R. R., Olson, H. G., Pratt, C. M., Amsterdam E. A., and Mason, D. T. Effects of beta-adrenergic blockade in coronary heart disease propranolol in angina pectoris. *Clin. Pharmacol. Ther.* 18:594, 1973.
  - 135 Frishman, W., Smith, L., Beller, B., Hughes, P., and Kilip, T. Noninvasive assessment of clinical response to oral propranolol therapy. *Am J Cardiol* 35:660, 1975.
  - 136 Guazzi, M., Fiorentini, C., Polese, A., Magnani, F., and Olivan, M. T. Treatment of continuous angina pectoris with beta blocking agents. *Br Heart J* 37:125, 1975.
  - 137 Shand, D. G. Propranolol. *N Engl J Med.* 293:107, 1975.
  - 138 Greenblatt D. J., and Hoch Waser J. Adverse reactions to propranolol in hospitalized medical patients: a report from the Boston Collaborative Drug Surveillance Program. *Am Heart J* 86:49, 1973.
  - 139 Arslan, M., Hallu V., and Wendelin H. Propranolol and LB 46 (prindolol) in angina pectoris. *Ann. Clin. Res.* 5:91, 1973.
  - 140 Aronow W. S., and Kaplan, M. A. Propranolol with isosorbide dinitrate versus placebo in angina pectoris. *N Engl J Med.* 280:847, 1969.
  - 141 Frickard, E. N. C., and Gillam P. M. S. Assessment of propranolol in angina pectoris. *Br Heart J* 33:473, 1971.
  - 142 Warren, S. G., Brewer D. L., and Organ E. S. Long term propranolol therapy for angina pectoris. *Am J Cardiol* 37:420, 1976.
  - 143 Morrell, H. W. Propranolol. *Ann Intern Med.* 78:913, 1973.
  - 144 Amsterdam E. A., Gorlin R., and Wolfson S. Evaluation of long term use of propranolol in angina pectoris. *JAMA* 210:103, 1969.



- ment of coronary vasomobility in the intact animal and man. *Chest* 60 522 1971
69. Sonnes M F and Shurey E K Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* 11 735 1962
  70. Ganz W and Marcus H S Failure of intracoronary nitroglycerin to alleviate pacing induced angina. *Circulation* 46 880 1972
  71. Ganz W and Marcus H S Changes in myocardial oxygen consumption during relief of pacing induced angina by nitroglycerin (Abstr.) *Am J Cardiol* 31 133 1973
  72. Luebs E D, Cohen A, Zaleski E J et al Effect of nitroglycerin, isosorbide dinitrate and papaverine on coronary blood flow in man measured by coincidence counting technique and rubidium 84. *Am J Cardiol* 17 535 1966
  73. Gorlin R, Brachfeld N, Macleod et al Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation* 19 705 1959
  74. Rowe G G, Chelous C J, Alfonso S et al Systemic and coronary hemodynamic effects of erythritol tetranitrate. *J Clin Invest* 40 1217 1961
  75. Fam W M and McGregor M Effects of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circ Res* 15 355 1964
  76. Horwitz L D, Gorlin R, Taylor W J et al Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease. *J Clin Invest* 50 1578 1971
  77. Becker L C, Fortuin N J and Pitt H Effect of ischemia and antiaanginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ Res* 28 263 1971
  78. Forman R, Kirk E S, Downey J M et al Nitroglycerin and heterogeneity of myocardial blood flow. *J Clin Invest* 62 905 1973
  79. Kattus A A, Alvaro A B and Coulson A Effective ness of isosorbide dinitrate and nitroglycerin in relieving angina pectoris during uninterrupted exercise. *Chest* 67 640 1975
  80. Gray H, Chatterjee K, Vyden J K et al The hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure. *Am Heart J* 90 346 1975
  81. Russek H I Therapeutic role of coronary vasodilators: glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate. *Am J Med Sci* 252 9 1966
  82. Klaus A, Zaret B, Pitt B et al Comparative evaluation of sublingual long acting nitrates in angina pectoris (Abstr.) *Am J Cardiol* 31 142 1973
  83. Bunn W H Jr and Chremos A N Clinical evaluation of sublingual nitrates: onset and duration of nitroglycerin and isosorbide dinitrate. *Angiology* 14 48 1963
  84. Riseam J E F, Koretsky B and Altman G E Stereoisomeric nitrates in the treatment of angina pectoris. *Am J Cardiol* 15 220 1965
  85. Sweatman T, Strauss G, Selzer A and Cohn K E The long acting hemodynamic effects of isosorbide dinitrate. *Am J Cardiol* 29 475 1972
  86. Winsor T, Kaye H and Mills B Hemodynamic response of oral long acting nitrates: evidence of gastrointestinal absorption. *Chest* 62 407 1972
  87. Needleman P, Blehm H J and Rotkoff A S Relationship between glutathione dependent denitration and the vasodilator effectiveness of organic nitrates. *J Pharmacol Exp Ther* 165 286 1968
  88. Goldstein R E and Epstein S E Nitrates in the prophylactic treatment of angina pectoris. *Circulation* 48 917 1973
  89. Aronow W S and Chewluk H M Sublingual isosorbide dinitrate therapy versus sublingual placebo in angina pectoris. *Circulation* 41 869 1970
  90. Livesley H, Catley P F, Campbell R C and Oram S Double blind evaluation of verapamil, propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris. *Br Heart J* 1 375 1973
  91. Mikulic E, Franciosa J A and Cohn J N Comparative hemodynamic effects of chewable isosorbide dinitrate and nitroglycerin in patients with congestive heart failure. *Circulation* 52 477 1975
  92. Glancy D L, Richter M A, Ellis E V and Johnson W Effect of swallowed isosorbide dinitrate on blood pressure, heart rate and exercise capacity in patients with coronary artery disease. *Am J Med* 62 39 1977
  93. Amsterdam E A, Swan N, Tonkin M, Wampold D, DeMaria A N and Mason D T Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral sustained nitroglycerin (Abstr.) *Circulation* 52 II 150 1975
  94. Thompson E J, Glass P and Arora J Measurement by invasive methods of the hemodynamic effects of sustained release nitroglycerin in patients with angina pectoris subjected to maximal stress (Abstr.) *Am J Cardiol* 31 162 1973
  95. Wendkos M H and Meshulam N Comparative effects of placebo and sustained-release nitroglycerin in anginal subjects. *J Clin Pharmacol* 13 160 1973
  96. Winsor T Experimental design for evaluation of antiaanginal nitrate drugs: evidence of efficacy (Abstr.) *Circulation* 48 IV 321 1973
  97. Davis T A and Wiseloff H H The treatment of angina pectoris with a nitroglycerin ointment. *Am J Med Sci* 230 259 1955
  98. Taylor W R, Forrester J E, Magnusson P, Takano T, Chatterjee K and Swan H J C The hemodynamic effects of nitroglycerin ointment in congestive heart failure (Abstr.) *Circulation* 52 II 36 1975
  99. Armstrong P W, Matthew M T, Boromand K and Parker J O Hemodynamic effects of nitroglycerin ointment in acute myocardial infarction (Abstr.) *Circulation* 52 II 152 1975
  100. Reichel N, Goldstein R E, Redwood D R and Epstein S E Sustained effects of nitroglycerin ointment in patients with angina pectoris. *Circulation* 50 348 1974
  101. Meister S G, Engel T R, Guha N, Furr C M, Festosa G S, Hart K and Frankl W S Sustained hemodynamic action of nitroglycerin ointment. *Br Heart J* 38 1031 1976
  102. Parker J O, Augustine R J, Burton J R, West R O and Armstrong P W Effect of nitroglycerin ointment on the clinical and hemodynamic response to exercise. *Am J Cardiol* 38 162 1976
  103. Paterson J W, Connolly M E, Dollery C T, Hayes A H and Cooper H G The pharmacodynamics and metabolism of propranolol in man. *Pharm Clin* 2 127 1970
  104. Thompson F D, Joekes A M and Foulkes D M Pharmacodynamics of propranolol in renal failure. *Br Med J* 2 434 1972
  105. Evans G W, Nies A S and Shand D G The disposition of propranolol: 3 Decreased half life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. *J Pharmacol Exp Ther* 186 114 1973
  106. Shand D G and Rangno R E The disposition of

# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

## Management of shock following acute myocardial infarction Part II Mechanical circulatory assistance

Leslie A. Kuhn M.D.  
New York, N.Y.

Several years have elapsed since the introduction of mechanical circulatory aids in the treatment of shock following acute myocardial infarction. We will attempt to summarize the effects of mechanical circulatory support, its usefulness in clinical conditions and probable future directions of its applications.

### Historical aspects

In 1953 Kantrowitz and Kantrowitz<sup>1</sup> demonstrated an increase in the total coronary flow of dogs by increasing aortic pressure in diastole by mechanical retardation of the aortic pressure pulse. Initially, counterpulsation of blood was utilized to provide mechanical assistance to the myocardium with diminished coronary flow and severe dysfunction. This augmented coronary flow in diastole by raising diastolic pressure and reduced pressure work of the left ventricle in systole by lowering aortic systolic pressure.<sup>2</sup> This has the obvious rationale of unloading the left ventricle and favorably altering the myocardial supply-demand relationship. Counterpulsation of blood, though possessed of an attractive rationale, required large bore cannulation of both femoral arteries. In addition, our own experiments indicated that the effects of counterpulsation of blood varied with the level of arterial pressure, normal systolic arterial pressure being reduced to a much greater extent than an initially depressed arterial pressure. When central aortic counterpulsation of blood was performed during

profound hypotension, there was only slight and inconsistent improvement of the hemodynamic abnormalities and anaerobic myocardial metabolic abnormalities associated with acute myocardial infarction and shock. However, when during central aortic counterpulsation an adequate central aortic pressure was maintained by phased or non-phased balloon obstruction of the lower abdominal aorta, anaerobic myocardial metabolic abnormalities were reversed and there were significant elevations of cardiac output, coronary perfusion pressure and coronary flow, with only slight increment of myocardial oxygen consumption.<sup>3</sup>

Balloon aortic counterpulsation was originally introduced by Mouloupoulos and associates, with essentially the same rationale as the earlier blood counterpulsation. Subsequent investigation by a large number of investigators, including Claus and associates<sup>4</sup> and Kantrowitz and associates,<sup>5</sup> demonstrated the advantages and practicality of this technique in humans with a variety of causes of diminished coronary flow and left ventricular failure, and thus is the technique most widely applied at present. It became apparent that intraaortic balloon counterpulsation was more effective than central aortic blood counterpulsation in reversing the hemodynamic abnormalities of shock following acute myocardial infarction and was more feasible to apply to a critically ill patient. The efficacy of the method in shock following acute myocardial infarction is probably more dependent on increasing a critically reduced coronary perfusion pressure and flow than in mere reduction in left ventricular work, which may not achieve significant proportions when there is marked hypotension. Although in general

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, N.Y.

Received for publication: March 19, 1978

Reprint requests: Leslie A. Kuhn, M.D., Division of Cardiology, Department of Medicine, The Mount Sinai School of Medicine, 1176 Fifth Avenue, New York, N.Y. 10029

- 145 Strauss H C, Gilbert M, Svenson R W, Miller H C and Wallace A G Electrophysiologic effects of propranolol on sinus node function in patients with sinus node dysfunction *Circulation* 54 452 1976
- 146 Frohlich, E D, Tarazi, H C and Dustan H P Peripheral arterial insufficiency: A complication of beta adrenergic blocking therapy *JAMA* 208 2471 1969
- 147 Allen R and Genovese B Propranolol withdrawal, *Ann Intern Med* 82 431 1975
- 148 Alderman E L, Coltart J, Wettach G E and Harrison D C Coronary artery syndromes after sudden propranolol withdrawal *Ann Intern Med* 81 625 1974
- 149 Nellen M Withdrawal of propranolol and myocardial infarction *Lancet* 1 558 1973
- 150 Langou R A, Wiles J C, Peduzzi, P N, Hammond G L and Cohen L S Incidence and mortality of perioperative myocardial infarction in patients undergoing coronary artery bypass grafting *Circulation* (In press)
- 151 Sloane R Withdrawal of propranolol and myocardial infarction *Lancet* 1 156 1973
- 152 Diaz R G, Somberg J C and Freeman E Withdrawal of propranolol and myocardial infarction *Lancet* 1 1968 1973
- 153 Hansten P D *Drug interactions* Philadelphia 1971 Lea & Febiger Publishers pp 12 74
- 154 Merin R B Anesthetic management problems posed by therapeutic advances III Beta adrenergic blocking drugs *Anesth Analg* 51 617 1972
- 155 Glick, G and Braunwald E Relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of the heart *Circ Res* 16 363 1965
- 156 MacAlpin H N, Kattus A A and Winfield M E Effect of a beta adrenergic blocking agent, Nethalide™ and nitroglycerin on exercise tolerance in angina pectoris *Circulation* 31 869 1965
- 157 Russek, H I Propranolol and isosorbide dinitrate synergism in angina pectoris *Am J Med Sci* 254 406 1967
- 158 Russek, H I Propranolol and isosorbide dinitrate synergism in angina pectoris *Am J Cardiol* 21 44 1968
- 159 Russek H I The natural history of severe angina pectoris with intensive medical therapy alone: a five year prospective study of 133 patients *Chest* 65 46 1974
- 160 Clausen J P and Trap-Jensen J Heart rate and arterial blood pressure during exercise in patients with angina pectoris Effects of training and of nitroglycerin *Circulation* 53 436 1976
- 161 Kennedy C L, Speikerman R E, Lindsay M I Jr, Mankin H T, Frye R L and McCallister B D One year graduated exercise program for men with angina pectoris *Mayo Clin Proc* 51 231 1976
- 162 Sun D N, and Neill W A Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning *J Clin Invest* 54 763 1974
- 163 Redwood D R, Roseng D R, and Epstein S E Circulatory and symptomatic effects of physical training in patients with coronary artery disease and angina pectoris *N Engl J Med* 286 959 1972
- 164 Detry J M, Rousseau M, Vandenbroucke G, Kusumi M S, Brasseur L A and Bruce R A Increased arteriovenous oxygen difference after physical training in coronary heart disease *Circulation* 44 109 1971
- 165 Wolfson E and Costin J C Physical conditioning as therapy for angina pectoris *Conn Med* 40 527 1976
- 166 Malmberg H O, Jansson S O and Hallvrouss G The effect of beta blockade and/or physical training in patients with angina pectoris *Curr Ther Res* 16 171 1974
- 167 Blackburn H, Taylor H L, Hamrell B, Buskirk E, Nicholas W C and Thorsen R D Premature ventricular complexes induced by stress testing *Am J Cardiol* 31 441 1973
- 168 Rechnitzer P A, Pichard H A, Pavia A V, Yuhaz M S and Cunningham D Long term follow up study of survival and recurrence rates following myocardial infarction in exercising and control subjects *Circulation* 45 853 1972
- 169 Bruce R A The benefits of physical training for patients with coronary heart disease Controversy in Internal Medicine Philadelphia 1974 W B Saunders Company pp 145-161
- 170 Wilhelmsson C, Vedin J A, Wilhelmsson L, Tibblin G and Werkö L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol, *Lancet* 2 1157 1974
- 171 Green K E, Chamberlain D A, Fulton R M, Hamer N A J, Oliver M F and Pentecost B L Improvement in prognosis of myocardial infarction by long term beta adrenoceptor blockade using practolol *Br Med J* 3 735 1975
- 172 Wolfson S, Rose L I, Bousser J E, Pansu A F, Acosta A, Cooper K H and Schecter E Serum enzyme levels during exercise in patients with coronary heart disease effects of training *Am HEART J* 84 478 1972
- 173 Clausen J P and Trap-Jensen J Effects of training on the distribution of cardiac output in patients with coronary artery disease *Circulation* 42 611 1970
- 174 Wolfson S, Acosta A W, Rose L I, Pansu A F and Engelman K Effects of conditioning on plasma catecholamine levels during exercise in patients with coronary artery disease (Abstr) *Am J Cardiol* 29 297 1972
- 175 Eckstein R W Effect of exercise and coronary artery narrowing on coronary collateral circulation *Circ Res* 5 230 1957
- 176 Tobis J S Programs for the rehabilitation of the coronary patient "Coronary Heart Disease Philadelphia 1971 J B Lippincott Company pp 323-328
- 177 Feinstein A R and Wells C K Two new indexes for assessing clinical improvement in angina pectoris *Trans Am Assoc Physicians* 88 161 1975
- 178 Feinstein A R and Wells C K A new clinical taxonomy for rating change in functional activities of patients with angina pectoris *Am HEART J* 90 127 1977
- 179 Tremblay G., Biron P and Proulx A Quantification pitfalls in comparative studies of antihypertensive therapies *Am HEART J* 89 521 1975
- 180 Redwood D R, Roseng D R, Goldstein R E, Beiser G D, and Epstein S E Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris *Circulation* 43 618 1971

# Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

## Management of shock following acute myocardial infarction Part II Mechanical circulatory assistance

Leslie A Kuhn MD  
New York NY

Several years have elapsed since the introduction of mechanical circulatory aids in the treatment of shock following acute myocardial infarction. We will attempt to summarize the effects of mechanical circulatory support, its usefulness in clinical conditions and probable future directions of its application.

### Historical aspects

In 1953 Kantrowitz and Kantrowitz<sup>1</sup> demonstrated an increase in the total coronary flow of dogs by increasing aortic pressure in diastole by mechanical retardation of the aortic pressure pulse. Initially counterpulsation of blood was utilized to provide mechanical assistance to the myocardium with diminished coronary flow and severe dysfunction. This augmented coronary flow in diastole by raising diastolic pressure and reduced pressure work of the left ventricle in systole by lowering aortic systolic pressure. This has the obvious rationale of unloading the left ventricle and favorably altering the myocardial "supply-demand" relationship. Counterpulsation of blood, though possessed of an attractive rationale, required large bore cannulation of both femoral arteries. In addition, our own experiments indicated that the effects of counterpulsation of blood varied with the level of arterial pressure, normal systolic arterial pressure being reduced to a much greater extent than an initially depressed arterial pressure. When central aortic counterpulsation of blood was performed during

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Received for publication March 3, 1978.

Reprint requests: Leslie A. Kuhn, MD, Division of Cardiology, Department of Medicine, The Mount Sinai School of Medicine, 116 Fifth Avenue, New York, NY 10029.

profound hypotension, there was only slight and inconsistent improvement of the hemodynamic abnormalities and anaerobic myocardial metabolic abnormalities associated with acute myocardial infarction and shock. However, when during central aortic counterpulsation an adequate central aortic pressure was maintained by phased or non-phased balloon obstruction of the lower abdominal aorta, anaerobic myocardial metabolic abnormalities were reversed and there were significant elevations of cardiac output, coronary perfusion pressure and coronary flow with only slight increment of myocardial oxygen consumption.<sup>2</sup>

Balloon aortic counterpulsation was originally introduced by Mouloupoulos and associates<sup>3</sup> with essentially the same rationale as the earlier blood counterpulsation. Subsequent investigation by a large number of investigators, including Claus and associates<sup>4</sup> and Kantrowitz and associates<sup>5</sup> demonstrated the advantages and practicality of this technique in humans with a variety of causes of diminished coronary flow and left ventricular failure and this is the technique most widely applied at present. It became apparent that intraaortic balloon counterpulsation was more effective than central aortic blood counterpulsation in reversing the hemodynamic abnormalities of shock following acute myocardial infarction and was more feasible to apply to a critically ill patient. The efficacy of the method in shock following acute myocardial infarction is probably more dependent on increasing a critically reduced coronary perfusion pressure and flow than in mere reduction in left ventricular work, which may not achieve significant proportions when there is marked hypotension. Although in general

left ventricular filling pressure is reduced by the use of intraaortic balloon pumping in experimental cardiogenic shock, this does not occur invariably and coronary flow is not invariably increased by this device despite raising central aortic diastolic pressure. This probably is due to peripheral adjustments in the coronary circulation during the myocardial ischemia of the shock state which may provide maximal dilatation, reversed to some extent when coronary flow is more adequate. Nevertheless, the technique generally achieves some favorable hemodynamic and cardiac metabolic alteration when used in clinical acute myocardial infarction and shock, similar in direction to experimentally obtained results in animals.

### Clinical studies

Reported results of the efficacy of intraaortic balloon pumping in shock following acute myocardial infarction have varied widely after initial enthusiastic reports of its therapeutic potential in this syndrome.<sup>8</sup> Survival has been reported to vary from 11 per cent<sup>8</sup> to a most optimistic 71 per cent.<sup>9</sup> Obviously to account for these enormous differences in reported efficacy of balloon pumping we must conclude that differences in criteria for the definition of 'shock' underlie the results. Where 'shock' is rather rigidly defined to include marked hypotension, 90 mm Hg or below, with the concomitant clinical signs of shock, the results are less good than when the definition of shock is more loosely applied with regard to systolic arterial pressure. Analysis of reported series indicates that this is indeed the case. Willerson and associates<sup>8</sup> report two reasonably long term survivors in 20 patients with acute myocardial infarction and shock undergoing intraaortic balloon pumping. Both of these had acute inferior infarction. The authors criteria for 'shock' included systolic arterial pressure of less than 85 mm Hg. In contrast, Lefemine and associates<sup>9</sup> reported survival in 10 of 14 patients with cardiogenic shock following acute myocardial infarction. A systolic pressure of less than 90 mm Hg was used as a criterion for 'shock'. However, they report that in five patients the blood pressure was raised above 90 mm Hg by pressor agents prior to insertion of the balloon and they state that most of the group had associated findings of oliguria, peripheral vasoconstriction and diaphoresis implying that some

did not. It would appear that they were treating less severe instances of left ventricular dysfunction. O'Rourke and associates<sup>10</sup> report nine patients surviving of 25 treated with the intraaortic balloon. In their study, shock rigidly defined was not successfully treated but when the definition of shock was 'modified' requiring that systolic arterial pressure be less than 100 mm Hg, survivals as indicated above were obtained. Hagemeyer and colleagues<sup>11</sup> demonstrated survival in six of eight patients with left ventricular failure and in seven of 17 patients with 'cardiogenic shock', but left ventricular filling pressures are not indicated and patients over 65 years of age were excluded, as were those with ischemic episodes within 36 hours prior to pump support and, at least in some shock of more than 6 hours duration. Johnson and associates<sup>12</sup> reported eight of 18 surviving cardiogenic shock treated with the intraaortic balloon pump without surgery. The definition of shock included systolic arterial pressure below 100 mm Hg. One survivor was subsequently shown to have had normal coronary arteries. The authors contrast this with their previous experience with medically treated patients, showing a 7 per cent survival but it is not clear that the definition of shock was identical in the two groups. Survival was more likely in inferior infarction, whereas those who survived intraaortic balloon pumping with anterior septal infarction remained severely disabled. Less sanguine results were reported by Scheidt and co-workers<sup>13</sup> in a cooperative study involving 87 patients from several institutions, in which a 17 per cent survival rate was indicated employing a more rigid definition of shock. Our own results at Mt Sinai Hospital New York are more in keeping with those of Willerson and colleagues previously cited,<sup>8</sup> with one or perhaps two reasonably long term survivors in 32 consecutively studied patients with acute myocardial infarction and shock rigidly defined (pressure of 90 mm Hg or below in systole with concomitant signs of shock). We excluded patients with surgically remediable ventricular septal rupture or mitral regurgitation and those in whom the shock could reasonably be ascribed to marked bradycardia, tachycardia or acute myocardial ischemia.

The largest series of patients to date has been studied over a period of several years by the Massachusetts General Hospital group and their findings have been published in several reports.<sup>14</sup>

At this writing they have studied about 140 patients. Analysis of 36 survivors from 120 patients (which included patients with surgically remediable ventricular septal defect and mitral regurgitation) includes 24 surviving after balloon pump support and surgery and 12 surviving with balloon support alone. No patient requiring balloon support with acute mitral regurgitation or ventricular septal rupture survived without surgery. No survivor showed previous transmural infarction. Fifty per cent of the survivors in the pump and surgical group had ventricular septal rupture or mitral regurgitation. All other survivors showed some correctable abnormality contributing to the depth of shock, including resistant arrhythmias, conduction abnormalities, pulmonary edema and hypoxemia, new ischemia and drug related myocardial depression. All the non surgical survivors were stabilized by the balloon pump within 24 hours and were independent of the balloon within 4 days. In the 50 per cent of the surgical survivors without ventricular septal rupture or mitral regurgitation, all but one stabilized within 24 hours but all remained balloon dependent.

The use of surgery to correct ventricular septal rupture or massive mitral regurgitation may add to the salvage rate as well. On occasion myocardial revascularization and infarctectomy and aneurysmectomy but the mortality rate remains high, well over 50 per cent and is considerably higher if the surgery must be performed within the first two weeks of the acute infarction. It is beyond the scope of this paper to discuss full details of patient selection and results of the few series reported in which surgery has been performed in cardiogenic shock but it is recognized that the intraaortic balloon pump provides a useful adjunct as circulatory support to stabilize the patient and permit appropriate hemodynamic measurements and angiography so that a decision as to the advisability and feasibility of cardiac surgery can be made. It is of most benefit in this regard and has the strongest rationale in suspected ventricular septal rupture and/or mitral regurgitation. By lowering the resistance to ventricular ejection the shunt across the ventricular septal defect as well as the degree of mitral regurgitation should be diminished.

Before considering the precise role of intraaortic balloon pumping in specific clinical situations it is appropriate to examine the reported complica-

tions of the technique. Here again reported incidence varies widely. Of course this may be due to differences in the stage of surgical training of those who perform the insertion of the balloon. One would logically expect fewer local complications where experienced surgeons insert the balloon in contrast to institutions where surgical residents in various stages of training perform the procedure. O'Rourke and associates detail eight significant complications in 30 patients (one leg ischemia, one wound infection, five femoral arterial thrombi and one small aortic dissection) some of which were long lasting or apparently life threatening. Lefemine and associates' report a 17 per cent complication rate in 86 patients with intraaortic balloon insertion and failure of passage through the iliac or femoral artery in 13 per cent. In some of these the balloon could be inserted through an aortic arch graft. However the complication rate was 50 per cent in patients with cardiogenic shock. Complications included femoral arterial obstruction requiring balloon removal, iliac arterial obstruction, ischemic necrosis of the calf, gangrene of one or both legs, aortic dissection and cardiac tamponade thought to be secondary to anticoagulation. Four patients had permanent damage to the legs due to ischemia and one required bilateral amputation. Serious arterial obstruction occurred in 10 per cent and there was one fatal complication (pericardial tamponade). Curtis and associates' report a 26 per cent complication rate in 34 patients including arterial insufficiency necessitating amputation, opposite extremity embolus, deep vein thrombosis, groin infection, groin hematoma and arterial insufficiency not requiring surgery. Nine per cent of patients in the series required surgical intervention because of the complications. Our own group has experienced a much lower significant complication rate. Perhaps this is attributable to one senior surgeon assuming continued responsibility over the course of several years for the surgical management of intraaortic balloon insertion. At any rate the possibility of significant complications particularly in patients with cardiogenic shock must be considered in arriving at a decision as to the use of the intraaortic balloon.

*When shall the intraaortic balloon be used?*

I think the answer to this question at present should be earlier than we are currently using it.

It is still not entirely clear that many lives are saved for the reasonably long term by the use of the balloon in acute myocardial infarction once the shock syndrome has developed although in general temporary hemodynamic benefit can be effected. Our own studies and those of others, previously cited would support a pessimistic view as to its potential for saving large numbers of lives in cardiogenic shock. Our investigation of 663 consecutive patients with acute myocardial infarction admitted to Mt Sinai Hospital New York, in an 18 month period showed a 4.2 per cent incidence of shock, reasonably rigidly defined (systolic arterial pressure below 90 mm Hg with concomitant clinical signs of shock, not attributable to hypovolemia, arrhythmias, or surgically remediable ventricular septal rupture or mitral regurgitation).<sup>13</sup> This low incidence (4.2 per cent compared to 10 to 15 per cent in previous studies) is attributed to probable prevention of shock by more intensive treatment of pre shock conditions of congestive heart failure without shock, arrhythmias, fluid deficits, and metabolic abnormalities. This leaves a residuum of patients with extensive acute and old myocardial infarction refractory to all treatment for the most part. The average age of these patients was 68 years. Only 2.4 per cent of the patients with acute infarction exhibited the shock syndrome and were less than 70 years of age. Ten patients (35 per cent of the group with shock, 1.5 per cent of those with acute myocardial infarction) were less than 65 years of age. There were only nine patients in an 18 month period who were less than 70 years of age and lived at least two hours after admission (a minimal time necessary for attempting emergency medical therapy and rendering the balloon pump operative). This was 1.4 per cent of our patients with acute myocardial infarction. Of 14 patients subjected to intraaortic balloon pump support and emergency revascularization surgery in some there were no survivors. Subsequently in a total of 30 patients with intraaortic balloon pumping for cardiogenic shock we have obtained one or perhaps two patients with reasonably long term survival. If we project the salvage rate of the largest series of patients studied to date predicted salvage from intraaortic balloon pumping alone would be one or two patients in an 18 month period. Predicted salvage from intraaortic balloon pumping plus revascularization and/or infarctectomy or aneurysmectomy would be about three

patients in this interval, assuming an age "cut off" of 70 years. From these results, it would appear that once the shock syndrome has developed unless it is attributable to a surgically remediable cause it is still associated with an extremely poor prognosis regardless of pharmacologic, mechanical, or surgical therapy, although a few patients may be salvaged with the intraaortic balloon. One cannot apply data derived from treatment with the intraaortic balloon on the patient with severe left ventricular failure without shock to those with shock. The medical therapy of those with left ventricular failure not in shock (or with rather loosely defined shock) is considerably more effective than in those with shock. There is no satisfactory randomized study establishing a higher rate of survival in patients in left ventricular failure without shock treated with balloon pump support as compared to rigorous medical therapy although the use of balloon pump support in such patients has an attractive rationale. The superiority or necessity of balloon pumping in the group without shock has not been established since there is a better prognosis than in the shock group when treated medically.

Our current approach is to offer the intraaortic balloon pump to patients in shock generally less than 70 years of age who do not respond to pharmacologic attempts to raise arterial pressure and to treat congestive heart failure and significant arrhythmias within a short period of time. The possible hazards of the procedure and poor prognosis with balloon pump support must be explained carefully to the patient and family. Patients who deteriorate on the balloon are not studied further. Those who are balloon dependent after a few days have coronary arteriography and left ventriculography performed and a recommendation made on this basis whether a surgical approach is warranted. The criteria for the latter are not precise but generally revolve around adequacy of some left ventricular function, presence or absence of a discrete aneurysm and bypassable coronary arterial obstructions. Of course those with ventricular septal rupture or high degree mitral regurgitation are offered surgery, as late as possible after the acute myocardial infarction, depending on clinical stability. For those who can be weaned from the balloon many advocate early angiographic study (with the balloon operative). My own preference has been to defer these procedures unless there is

thought to be a ventricular septal rupture or mitral regurgitation because of the high degree of surgical risk in performing coronary bypass surgery infarctectomy or aneurysmectomy early after acute myocardial infarction

A question frequently asked is whether a community hospital without cardiac surgical or angiographic facilities should offer balloon pumping to its patients. This is not answered easily but from our own figures predicted salvage would be quite low for the patient in shock and therefore the number of patients so benefited would be very small. Of course the balloon pump may be used for other purposes on occasion such as refractory ventricular tachycardia or recurrent severe myocardial ischemia but here too the number of patients benefited would be small. It would appear more rational for such institutions to group their efforts so that perhaps each region might have a balloon pump available.

#### Future trends

Because of dissatisfaction with current survival rates with the balloon pump once the shock syndrome has developed it is reasonable to explore other modalities of circulatory support or the use of the balloon pump in pre shock states in an effort to prevent the shock syndrome. There has been considerable investigation of the concept of preservation of ischemic myocardium and indeed infarct size as judged by ST segment elevation and CPK release from the myocardium can be reduced by intraaortic balloon pumping in an experimental setting.<sup>6</sup> Whether or not intraaortic balloon pumping can prevent shock in humans with acute myocardial infarction has not been determined but it is accepted that the shock syndrome is associated with extensive left ventricular infarction both old and recent in various stages of development so it is conceivable that preserving ischemic myocardial tissue may prevent critical degrees of necrosis leading to the shock syndrome. As a practical matter it is unlikely that the technique will be applied to good risk patients because of the possible complications of the procedure and the acceptable prognosis without balloon pumping. However hemodynamic subsets have been defined with accompanying prognoses. It would appear most rational to apply the intraaortic balloon pump to those patients not in shock who have severe left ventricular dysfunction and a poor

prognosis but this should be studied in a careful randomized manner so that appropriate conclusions can be drawn as to the efficacy of the balloon in preventing the development of shock and improving the eventual prognosis. Such data are not available at this time.

Other techniques of circulatory support may be useful in the future but none has been tested sufficiently to have established itself as superior to the intraaortic balloon. External counterpulsation has the advantage of a non invasive technique and hence should avoid the vascular complications of the intraaortic balloon. Although there is some evidence that the myocardial supply-demand ratio may be favorably affected by this technique,<sup>7</sup> hemodynamic studies have shown much less reduction of the elevated left ventricular filling pressure in acute myocardial infarction with severe left ventricular dysfunction when extracorporeal counterpulsation is employed than when intraaortic balloon pumping is utilized. A recent cooperative trial of external counterpulsation was reported to be of benefit in reducing the mortality rate of patients with clinical Class II acute myocardial infarction (mild congestive heart failure). However in this study investigating a group with relatively good prognosis no hemodynamic measurements were obtained in the treated and untreated groups so that accurate assessment of the efficacy of the device is not possible. It is unlikely however that the extracorporeal technique will be of sufficient efficacy to affect the clinical course of the patient already in shock but it is possible though by no means established that it may be of prophylactic benefit in certain hemodynamic subsets.

Techniques of left ventricular bypass are more effective in unloading the failing left ventricle than is the intraaortic balloon pump and such techniques may be helpful in reversing and preventing ventricular fibrillation in acute myocardial infarction.<sup>10</sup> Long lasting and effective left ventricular bypass in postoperative patients with open chest cannulation of the left atrium and aorta has been obtained by Litwak and associates.<sup>11</sup> Other left ventricular assistance devices are being studied and it is probable that relatively long term left ventricular bypass will be feasible and effective. In instances of severe left ventricular dysfunction due to acute myocardial infarction unresponsive to medical measures and intraaortic balloon pumping prolonged and effec-



tive circulatory support may be possible following open chest aortic and left ventricular or left atrial cannulation

## Conclusions

Intraaortic balloon pumping may provide temporary hemodynamic benefit in acute myocardial infarction with shock but reports have differed rather widely concerning its efficacy in providing long term survival. Much of this variation depends on differing criteria for the definition of "shock." Low survival rates are obtained when the syndrome is rigidly defined, but rates are considerably higher when patients with systolic arterial pressures higher than 90 mm Hg are included. The intraaortic balloon is of considerable efficacy in stabilizing the patient with a surgically remediable cause for the shock syndrome, such as ruptured interventricular septum or massive mitral regurgitation. Survival rate is low even with the intraaortic balloon when shock is present in the absence of such conditions, although there may be slight additional salvage with emergency revascularization and/or infarctectomy and aneurysmectomy.

The complication rate of intraaortic balloon insertion is not inconsiderable with some studies showing about a 17 per cent incidence but with a much higher rate (as much as 50 per cent) in patients with cardiogenic shock. These include arterial insufficiency of the lower extremities, infection, hematomata, occasionally dissection of the aorta, and arterial occlusions necessitating amputations. Death due to the procedure is quite rare.

It is not clear whether the balloon pump improves survival in patients with severe left ventricular failure who are not in shock and do not have ruptured interventricular septum or advanced mitral regurgitation because the medical management of such patients provides much better results than it does in patients with shock. It would be necessary to perform studies of randomized patients with and without circulatory support in these hemodynamic subgroups to determine the true efficacy of the balloon pump in patients with severe heart failure but not in shock.

Analysis of the patient population with shock following myocardial infarction indicates that the incidence of shock is declining probably because of better methods of treating congestive heart

failure, arrhythmias, and metabolic derangements. The average patient is of advanced age with a history of previous myocardial infarction. The number of patients who reasonably can be expected to survive because of intraaortic balloon pumping is small once the shock syndrome has developed.

Because of the poor results with all modalities of treatment once the shock syndrome is apparent, attention should be directed to attempts to prevent shock and to other means of circulatory support. It is not known whether shock can be prevented but use of the intraaortic balloon pump in poor risk patients who are not in shock as determined by hemodynamic measurements should be studied intensively for this purpose. Techniques of left ventricular bypass to provide long lasting circulatory support may be fruitful in reducing mortality in patients with cardiogenic shock or in those with severe left ventricular failure.

## REFERENCES

- 1 Kantrowitz A and Kantrowitz A. Experimental augmentation of coronary flow by retardation of the arterial pressure pulse. *Surgery* 34:678, 1953.
- 2 Claus R H, Birtwell C, Alberthal G, et al. Assisted circulation I. The arterial counterpulsator. *J Thorac Cardiovasc Surg* 41:447, 1961.
- 3 Kuhn L A, Unger A, Novick S, et al. Effects of combined central aortic counterpulsation and balloon aortic obstruction in myocardial infarction with shock. *Circulation* 38:VI 120, 1968.
- 4 Mouloupos S D, Topaz S and Koff W J. Diastolic balloon pumping (with carbon dioxide) in the aorta. A mechanical assistance to the failing circulation. *AM HEART J* 63:660, 1962.
- 5 Kantrowitz A, Tonneland S, Freed P S, et al. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA* 203:113, 1968.
- 6 Willerson J T, Curry G C, Watson J T, et al. Intraaortic balloon counterpulsation in cardiogenic shock: medically refractory left ventricular failure and/or recurrent ventricular tachycardia. *Am J Med* 58:183, 1975.
- 7 Lefemine A A, Kosowsky B, Madoff I, et al. Results and complications of intraaortic balloon pumping in surgical and medical patients. *Am J Cardiol* 40:416, 1977.
- 8 O'Rourke M F, Chang V P, Windsor H M, et al. Acute severe cardiac failure complicating myocardial infarction. *Br Heart J* 37:169, 1975.
- 9 Hagemeyer F, Laird J D, Haalebos M M P, et al. Effectiveness of intraaortic balloon pumping without cardiac surgery for patients with severe heart failure secondary to a recent myocardial infarction. *Am J Cardiol* 40:951, 1977.
- 10 Johnson S A, Scanlon P J, Loeb H S, et al. Treatment of cardiogenic shock in myocardial infarction by intraaortic balloon counterpulsation. *Am J Med* 62:677, 1977.
- 11 Schedt S, Wilner G, Mueller H, et al. Intraaortic

- balloon counterpulsation in cardiogenic shock. Report of a cooperative clinical trial. *N Engl J Med* 288:979-983, 1973
12. Dunkman W B, Leimbach R C, Buckley M J et al. Clinical and hemodynamic results of intraaortic balloon pumping and surgery for cardiogenic shock. *Circulation* 46:465, 1972
13. Leimbach, R. C, Gold H K, Buckley M J et al. Identifying features of survivors from cardiogenic shock treated with intraaortic balloon pumping. *Am J Cardiol* 37:151, 1976
14. Curtis J J, Barnhorst D A., Pluth J R et al. Intraaortic balloon assist. *Mayo Clin Proc* 52:723-737, 1977
15. Kuhn L. A. Clinical management of cardiogenic shock. *Bull. N Y Acad Med* 56:366, 1974
16. Maroko P R, Bernstein E F, Libby P et al. Effects of intraaortic balloon counterpulsation on the severity of myocardial ischemic injury following acute coronary occlusion. *Circulation* 45:1150, 1972
17. Ratshin R A, Rackley C H and Russell R O Jr. Hemodynamic evaluation of left ventricular function in shock complicating myocardial infarction. *Circulation* 45:127, 1972
18. Banas, J E, Brilla A., Siroff H S., et al. Evaluation of external counterpulsation for the treatment of severe angina pectoris. *Circulation* 46:1174, 1972
19. Kuhn L. A., Lajam F., Sakurai, H et al. Successful defibrillation with the use of left ventricular drainage after prolonged refractory ventricular fibrillation in experimental acute myocardial infarction. *Am J Cardiol* 30:248, 1972
20. Litwak, H S., Lajam F., Kofsky R B et al. Obtained permanent left atrial and aortic cannulae for assisted circulation after cardiac surgery. *Trans Am Soc Artif Intern Organs* 19:243, 1973
21. Reeves T J, Winks, J R, Cox J R., et al. Mechanically assisted circulation. The status of the NHLBI program and recommendations for the future. Report of cardiology advisory committee. *Artif Organs* 1:39, 1977

## Definition of terms related to cardiac rhythm

WHO/ISC Task Force\*

Utrecht The Netherlands and New York N Y

In recent years several individuals and working groups have been concerned with definition and classification of electrocardiographic findings. Several factors, notably increasing international communication, exchange of data and introduction of new techniques like computer aided interpretation of the electrocardiogram have promoted the need for common language in electrocardiology.

A joint initiative of Dr E Dekker, Medical Director of the Dutch Heart Foundation (DHF) and Dr Z Pasa, Chief Cardiovascular Diseases of the World Health Organization (WHO) resulted in an international Task Force composed of members of various cardiological societies. Sponsored by WHO and the International Society of Cardiology with financial support from the Dutch Heart Foundation (DHF) this working group has been concerned primarily with the definition of terms related to cardiac rhythm. The results are presented in the format of a glossary arranged in alphabetical order and composed of two sections. The first part consists of acceptable terms and synonyms while in the second part a

list of non preferred terms is given (NPT). Reasons for discouragement and preferable synonyms have been given. With few exceptions, only those terms have been defined that are commonly used in clinical electrocardiography and clinical electrophysiology and which have bearing on the classification of arrhythmias. Many terms which primarily relate to anatomical structures and basic electrophysiological events have not been defined.

Definitions are given in general terms preferably with their specific electrocardiographic meaning. Since quantitative data may be related to special circumstances like age, technique of recording etc, they have when possible, been avoided. Likewise mechanisms of arrhythmias have not been included in the definitions of specific disorders of rhythm although some of them have been considered separately.

While the committee realizes the need for updated specifications of recording equipment it considers this aspect beyond the scope of its assignment.

This report as a draft served as a working document for Task Force I of the tenth Bethesda Conference on Optimal Electrocardiography of the American College of Cardiology (ACC). Several amendments of the ACC group have been incorporated in our report and care has been taken to avoid major inconsistencies in the terminology of the two groups.

### LIST OF ACCEPTABLE TERMS & SYNONYMS Aberrant conduction

The abnormal spread of an impulse through the normal or expected pathway resulting in an altered ECG wave form. Aberrant conduction may occur in the ventricles or within the atria. In cases of altered intraventricular conduction of supraventricular impulses it is preferred to reserve the term for conduction over the normal

From the Department of Cardiology, University Hospital Utrecht, The Netherlands and the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N Y.

Supported by a grant from the Dutch Heart Foundation.

Received for publication July 26, 1977.

Reprint requests: Etienne O Robles de Medina, MD, Department of Cardiology, University Hospital 101 Catharynesingel, Utrecht, The Netherlands.

Etienne O Robles de Medina, MD (Editor), Dept. of Cardiology, University Hospital Utrecht, The Netherlands; Roland Bernard, MD, Society on Medical Research of the EEC; Philippe Coumel, MD, French Society of Cardiology; Anthony N Damato, MD, American Heart Association; Charles Fisch, MD, American College of Cardiology; Dennis Frankler, MD, British Cardiac Society; Nicola A Mazur, MD, Cardiological Society of the USSR; Fris L Meyler, MD, Dutch Heart Foundation; Lars Mogensen, MD, Swedish Society of Cardiology; Pierre Moret, MD, International Society of Cardiology; Zbynek Pasa, MD, World Health Organization; Hein J J Wellens, MD, European Society of Cardiology.

pathway thus excluding conduction over accessory pathways as in the Wolff Parkinson White Syndrome (WPW). Furthermore use of the term aberrant conduction only seems meaningful if a rate related or other functional mechanism underlies the altered spread of excitation.

#### Abortive re-entry

See re-entry

#### Accelerated rhythm

Three or more consecutive impulses occurring at a rate of less than 100/min but greater than the inherent rate of that pacemaker. In each case the rate and site of impulse formation should be indicated (See also inherent rate).

#### Advanced (second degree) block

A form of second degree block in which alternate or two or more consecutive impulses fail to be conducted. Thus advanced block encompasses 2:1, 3:1, 4:1 block etc. (See second and third degree block).

#### Alternating rhythms

Impulse formation at two or more different sites in which one rhythm alternates with the other. Each rhythm should be specified separately e.g. sinus rhythm alternating with paroxysmal atrial fibrillation or sinus rhythm alternating with episodes of accelerated ventricular rhythm in which the latter is conducted retrogradely to the SA node (See also dual multifocal and multiple rhythm).

#### Anterograde (orthograde) conduction

Conduction of a cardiac impulse in a forward direction from the atria or atrioventricular (AV) junction to the ventricles. Anterograde indicates directional movement and is therefore preferred over antegrade in which ante denotes a forward position as in antechamber (See also retrograde conduction).

#### Arrest

Cessation of electrical activity of the heart or part of it. Arrest may be caused by different electrophysiological mechanisms. Although not always possible it is desirable to distinguish arrest from the pause in manifest electrical activity caused by exit block.

#### Arrhythmia

Any cardiac rhythm other than normal sinus rhythm. Such a rhythm may be either of sinus or ectopic origin and either regular or irregular. An arrhythmia may be due to a disturbance in impulse formation or conduction or both. It is preferred to use the term arrhythmia only as a general heading and not as a synonym for irregular impulse formation. Thus use of the term sinus arrhythmia is discouraged. It seems better to characterize a rhythm by the adjectives regular or irregular. For the same reason the term tachyarrhythmia should be avoided.

#### Atrial dissociation

A dual atrial rhythm in which two simultaneously active pacemakers do not affect each other's activity or rhythmicity (See also dual rhythm).

#### Atrioventricular (AV) block

The independent activation of atria and ventricles by differently originating impulses. Activation of the atria may arise from the SA node, the atria or the AV junction, while ventricular activation arises from the AV junction or the ventricles. Dissociation may occur for single activations or it may last longer. In the presence of captures dissociation is incomplete. When there are no captures during the time of recording dissociation is considered to be complete. AV dissociation is a descriptive term which does not obviate the need to look for the underlying mechanism(s). It should not be used as a synonym for complete AV block which may be one of the underlying mechanisms of AV dissociation (See also dual multifocal and multiple rhythm and parasystole).

#### Bigeminy

A repetitive pattern of two relatively closely spaced activations usually followed by a longer interval. Several mechanisms—which should be specified if possible—may underlie bigeminy. In its most common form the second impulse of the pair is an extrasystole (extra systolic bigeminy) (See also trigeminy).

#### Block

Delay or failure of impulse propagation. Varying degrees of conduction disturbance may occur anywhere in the heart in both the antero-

grade and retrograde directions (See also *entrance and exit block AV and VA block, first, second and third degree block*)

### **Bradycardia**

Three or more consecutive impulses from the same pacemaker at a rate less than the lower limit of its inherent rate (See also *accelerated rhythm and tachycardia*)

### **Bundle branch block (BBB)**

Delay or failure of conduction within a bundle branch BBB may be complete, incomplete permanent or intermittent (nonpermanent)

#### **Bundle branch block complete (CBBB)**

CBBB indicates either absence of conduction in a bundle branch, or delay of such magnitude that ventricular activation occurs largely or exclusively through the contralateral bundle, this causes widening of the QRS complex to 0.12 seconds or more

#### **Bundle branch block incomplete (IBBB)**

IBBB indicates delay in activation of a ventricle resulting from delayed conduction within the ipsilateral bundle branch. The involved ventricle may be partially activated by the impulse from the contralateral bundle

#### **Bundle branch block intermittent (nonpermanent)**

This indicates intermittence of a BBB pattern (See also *aberrant conduction and permanent BBB*)

#### **Bundle branch block permanent**

A BBB pattern which is always present and at all heart rates

### **Capture**

Usually premature activation of either the atria (atrial capture), by a retrogradely conducted ventricular or junctional impulse, or of the ventricles (ventricular capture), by an antegradely conducted supraventricular impulse. Captures are most commonly seen during episodes of AV dissociation. They should be distinguished from other types of premature impulses (See also *extrasystole*). The occurrence of a capture at a time when the atria or ventricles

have already been partially activated by another pacemaker impulse results in a *mixed or fusion complex*, also called *partial or incomplete capture* (See *fusion complex*)

### **Cardiac electrogram (CEG)**

A uni or bipolar record of electrical activity of the heart, taken with the electrode(s) within a cavity of the heart or in contact with the myocardium (direct leads) e.g. intracavitary EG, epicardial EG, etc

CEG's can be further defined according to the position and proximity of the recording electrodes to a given structure. Thus, intracavitary electrograms may be recorded from the right or left atrium (high or low), from the region of the atrioventricular (AV) junction (AV junctional EG), from the ventricles etc

An AV junctional EG may be labelled a *His bundle electrogram (HBE)* when a His bundle deflection is recorded. If this is not the case, the record should be called an *AV junctional EG* (See also *electrocardiogram*)

### **Complete block**

See *third degree block*

### **Concealed conduction**

Partial penetration of an impulse into the AV conduction system or a pacemaker-myocardial junction, which exerts an influence on subsequent impulse formation or conduction, or both

In a surface ECG lead the penetration of a blocked impulse into a specific structure can only be inferred from its effect on subsequent events

With intracavitary (e.g. an HBE) or intracardiac electrograms it is sometimes possible to demonstrate penetration of the blocked impulse to the level of recording. In such cases the impulse is not concealed at that level

### **Concealed re entry**

See *re entry*

### **Conduction ratio**

The ratio of the number of impulses that are formed to the number of impulses which are completely propagated. This ratio may be constant throughout the record, or it may vary (variable conduction ratio indicating variable

degrees of block) Wherever applicable the conduction ratio should be specified

### Coupling interval

The time relationship between two designated events in the cardiac cycle which are presumed to be linked (coupled) to one another This time relationship may be fixed or constant or it may vary (variable coupling) However in cases of independent rhythms (eg continuous AV junctional or ventricular parasystole with retrograde block of parasystolic impulses) when the activity of neither pacemaker is linked to that of the other the term varying coupling interval to denote variable intervals between activations from the two pacemakers is inappropriate

### Designation of cardiac electrogram deflections

Deflections in the CEG are labelled according to the electrical activity they are presumed to represent

SAN = sinoatrial nodal deflection

AVN = atrioventricular nodal deflection

A = atrial deflection

H = His bundle deflection

V = ventricular deflection

RB = right bundle branch deflection

LB = left bundle branch deflection

Recordings of SA and AV nodal activities have not been universally accepted

### Designation of electrocardiographic deflections

P = atrial activation

QRS = ventricular activation

ST T = ventricular repolarization

U = origin uncertain possibly terminal phase of Purkinje fiber repolarization

### Dual (double) rhythm

The simultaneous and independent occurrence of two rhythms Simultaneous activity of two pacemakers implies that the one with the slower rate of discharge is protected against the impulses of the faster one The protection can be located within the pacemaker-myocardial junction (as in parasystole) within the myocardium (as in atrial dissociation) or within the AV conduction system (AV dissociation) Each rhythm should be specified separately (See also *alternating multifocal and multiple rhythm*)

### Echo

Return of an impulse to its chamber or area of origin This results in an atrial or ventricular echo respectively The reentrant pathway may be within the chamber of origin or other portion of the heart (See *reciprocal or reentrant impulse*)

### Electrocardiogram (ECG)

A uni or bipolar record of electrical activity of the heart taken with the electrodes outside a cardiac cavity and not in contact with the myocardium (surface or indirect leads) eg esophageal ECG body surface ECG If His bundle activity is recorded with body surface leads this should be called a His bundle ECG (See also *cardiac electrogram*)

### Entrance block

Delayed or failed penetration of an impulse into a pacemaking center When an impulse fails to penetrate and reset (discharge) a pacemaker the latter is said to be protected When there is delayed or only occasional resetting protection is incomplete (See also *exit block*)

### Escape (impulse or discharge)

Up to two consecutive impulses (SA nodal atrial AV junctional or ventricular) arising from the same or occasionally from different pacemaker(s) as a result of undue delay in the formation or arrival of the expected impulse of the prevailing rhythm (See also *escape rhythm and premature impulse*)

### Escape rhythm

Three or more consecutive escapes

### Exit block

Delay or failure of an impulse to reach or discharge the myocardium surrounding a pacemaker This definition also applies to sinoatrial conduction (See also *entrance block*)

### Extrasystole

A premature impulse which usually shows a fixed (and probably causal) relationship to the preceding activation of the same cardiac chamber Extrasystoles may also be induced electrically or mechanically in such cases a causal relationship to the preceding activation is usually

grade and retrograde directions (See also *entrance and exit block AV and VA block, first second and third degree block*)

### **Bradycardia**

Three or more consecutive impulses from the same pacemaker at a rate less than the lower limit of its inherent rate (See also *accelerated rhythm and tachycardia*)

### **Bundle branch block (BBB)**

Delay or failure of conduction within a bundle branch BBB may be complete incomplete permanent or intermittent (nonpermanent)

### **Bundle branch block complete (CBBB)**

CBBB indicates either absence of conduction in a bundle branch, or delay of such magnitude that ventricular activation occurs largely or exclusively through the contralateral bundle, this causes widening of the QRS complex to 0.12 seconds or more

### **Bundle branch block incomplete (IBBB)**

IBBB indicates delay in activation of a ventricle resulting from delayed conduction within the ipsilateral bundle branch The involved ventricle may be partially activated by the impulse from the contralateral bundle

### **Bundle branch block intermittent (nonpermanent)**

This indicates intermittence of a BBB pattern (See also *aberrant conduction and permanent BBB*)

### **Bundle branch block permanent**

A BBB pattern which is always present and at all heart rates

### **Capture**

Usually premature activation of either the atria (atrial capture), by a retrogradely conducted ventricular or junctional impulse or of the ventricles (ventricular capture), by an anterogradely conducted supraventricular impulse Captures are most commonly seen during episodes of AV dissociation They should be distinguished from other types of premature impulses (See also *extrasystole*) The occurrence of a capture at a time when the atria or ventricles

have already been partially activated by another pacemaker impulse results in a *mixed or fusion complex*, also called *partial or incomplete capture* (See *fusion complex*)

### **Cardiac electrogram (CEG)**

A uni or bipolar record of electrical activity of the heart taken with the electrode(s) within a cavity of the heart or in contact with the myocardium (direct leads), e.g., intracavitary EG, epicardial EG, etc

CEG's can be further defined according to the position and proximity of the recording electrodes to a given structure Thus, intracavitary electrograms may be recorded from the right or left atrium (high or low), from the region of the atrioventricular (AV) junction (AV junctional EG), from the ventricles, etc

An AV junctional EG may be labelled a *His bundle electrogram (HBE)* when a His bundle deflection is recorded If this is not the case, the record should be called an *AV junctional EG* (See also *electrocardiogram*)

### **Complete block**

See *third degree block*

### **Concealed conduction**

Partial penetration of an impulse into the AV conduction system or a pacemaker-myocardial junction, which exerts an influence on subsequent impulse formation or conduction, or both

In a surface ECG lead the penetration of a blocked impulse into a specific structure can only be inferred from its effect on subsequent events

With intracavitary (e.g. an HBE) or intracardiac electrograms it is sometimes possible to demonstrate penetration of the blocked impulse to the level of recording In such cases the impulse is not concealed at that level

### **Concealed re entry**

See *re entry*

### **Conduction ratio**

The ratio of the number of impulses that are formed to the number of impulses which are completely propagated This ratio may be constant throughout the record or it may vary (*variable conduction ratio* indicating variable

where the premature complex arises. The conduction time of the impulse immediately following the premature discharge is usually prolonged due to concealed conduction of the premature impulse.

### Intervals in the cardiac electrogram (CEG)

Since the technique of recording a CEG may differ it is necessary to indicate whether a uni or bipolar lead was used, the inter electrode distance, the filter frequency, used the frequency response of the recording equipment and the points at which interval measurements are made. If under specific circumstances the intrinsic deflection is used in measuring intervals in CEG's this should be clearly stated. Normal values should be given for each laboratory.

**PA** from the earliest onset of the P wave in any of the simultaneously recorded ECG leads to the onset of A in the CEG (HBE)

**PH** from the earliest onset of the P wave in any of the simultaneously recorded ECG leads to the onset of H in the HBE

**AH** from the onset of A to the onset of H in the HBE

**HV** from the onset of H to the onset of V in the HBE

**HQ HR** from the onset of H in the HBE to the earliest onset of Q or R in any of the simultaneously recorded ECG leads

**RB V RB Q and LB V LB Q** defined in the same way as HV and HQ respectively

### Intervals in the electrocardiogram

It is customary to measure these intervals in the limb leads

**PQ or PR interval** from the earliest onset of the P wave to the earliest onset of the Q or R wave of the QRS complex

**PQ or PR segment** from the end of the P wave to the onset of the QRS

**P width** from the onset of the end of the widest P wave

**QRS width** from the onset of the end of the widest QRS complex

**QT interval** from the onset of Q or R to the end of the T wave

### Intra atrial conduction delay

Conduction delay within the atria resulting in abnormal widening and/or distortion of the P wave in the ECG

### Longitudinal dissociation

The presence of dissimilar conduction and excitability properties in dual conduction pathways that have common proximal and distal common connections. One pathway ( $\beta$ ) displays a long refractory period and fast conduction velocity while the reverse holds true for the other pathway ( $\alpha$ )

### Mobitz type I block

See *second degree block type I*

### Mobitz type II block

See *second degree block type II*

### Multifocal (multiform) rhythm

A rhythm of either supraventricular or ventricular origin which is characterized by varying cycle lengths and morphologies of the activation waves. Such a rhythm should further be specified according to the rate of impulse formation. Multifocal configuration of the waves may point to multifocal origin although this is not necessarily the case (See *alternating dual and multiple rhythm* and also *chaotic rhythm* and *wandering pacemaker NPT*)

### Multiple rhythm

The simultaneous and independent occurrence of two or more rhythms e.g. dual (double) triple or quadruple rhythms. Each of these should be specified separately (See also *alternating dual and multifocal rhythm*)

### Nonspecific intraventricular block

Any type of intraventricular conduction disturbance that cannot be completely ascribed to block in the specific conduction system (See also *arborization block intramural conduction disturbance myofibrillar parietal and peri infarction block NPT*)

### Orthograde conduction

See *anterograde conduction*

### Pacemaker

A group of cardiac fibers initiating one or more activations. This definition does not take into account the various mechanisms which may be involved in the generation of a cardiac impulse. From the electrophysiological point of view, the term is not restricted to an anatomically identifiable



absent (See also *capture echo and premature impulse*)

### Fascicular block

Fascicular block is an electrocardiographic (electrophysiologic) concept ascribed to a conduction defect in one of the fascicles of the left bundle branch (See *fascicular block anterior and posterior*). As yet the ECG pattern of block in the (mid) septal fascicle of the left bundle branch is not well known. Although the concept of fascicular block proves very useful and is indeed widely accepted, precise well defined anatomical correlates have not been identified.

### Fascicular block (left) anterior

The ECG concept of block in the anterior fascicle of the left bundle branch as the basis of delayed activation of the anterolateral wall of the left ventricle (See also *fascicular block*)

### Fascicular block (left) posterior

The ECG concept of block in the posterior fascicle of the left bundle as the basis of delayed activation of the posterior wall of the left ventricle (See also *fascicular block*)

### Fibrillation

Irregular, disorganized electrical activity of atria or ventricles. In *atrial fibrillation* P waves are absent and the baseline consists of irregular waveforms which continuously change in shape, duration, amplitude, and direction. In the absence of advanced or complete AV block, the resulting ventricular response is totally irregular (random). In *ventricular fibrillation* QRS and T waves can no longer be identified. The recorded deflections continuously change in shape, duration, magnitude and direction.

### First degree block

Delayed conduction with a 1:1 conduction ratio. In any individual case the conduction time should be specified (See also *second and third degree block*)

### Flutter

Rapid and regular electrical activity of atria or ventricles which is characterized in at least one ECG lead by the absence of an isoelectric line between the deflections of the *fluttering chamber*.

In *atrial flutter* the rate of the atria is usually in the range of 200-350/minute. Some distinguish between *typical* and *atypical* forms of atrial flutter. In the typical variety the tracing displays a saw tooth appearance in Leads II and III while this is not the case in the atypical form. The distinction between the atypical form of atrial flutter and atrial tachycardia with a rapid rate is not always possible.

In *ventricular flutter*, the ventricular rhythm is regular, the rate usually exceeds 250/minute and, the components of QRS and T cannot be identified or separated.

### Fusion (mixed) complex

#### See capture

Simultaneous or near simultaneous activation of either atria or ventricles (atrial or ventricular fusion complex respectively) by impulses coming from different directions. This results in an electrocardiographic complex which is intermediate (mixed) in form between the deflections resulting from activation by each single impulse.

### Gap in conduction

A period in the cardiac cycle during which there is absence of conduction, whereas conduction occurs with impulses of greater and lesser prematurity. Gap in conduction is usually seen during AV or VA transmission, but it probably also occurs in other parts of the heart.

### Incomplete (partial) block

Is a definition encompassing first and second degree block.

### Inherent rate

The frequency of impulse formation which is generally attributed to a given pacemaker localization. The inherent rate may differ according to age or other factors. For adults the following values are thought to be representative:

SA node 50-100/min

atrium not well known probably 40-65/min

AV junction 40-60/min

ventricle 35-40/min

### Interpolation

The phenomenon in which a premature impulse usually of ectopic origin occurs between two consecutive impulses of another pacemaker both of which are conducted to the chamber.

in the cardiac cycle during which a premature impulse is conducted more slowly than one falling outside the refractory period ( $P_r$ ,  $P_r$  in Fig 1)

**Functional refractory period (FRP)** The shortest possible ventricular or atrial interval resulting from two consecutively conducted atrial or ventricular activations respectively. For the anterograde conduction this interval is indicated by QRS<sub>1</sub> in Fig 1

### Retrograde conduction

Conduction of a cardiac impulse in a reverse direction usually used to indicate ventriculo atrial conduction (See also *anterograde conduction*)

### Second degree block

A conduction disturbance in which not every impulse is completely propagated from its site of origin. The term second degree block should only be applied during sustained impulse formation. Thus it should not be used in cases of non-conducted premature impulses (See also *conduction ratio*)

**Second degree block type I (Wenckebach) (Mobitz type I)** Intermittent failure of impulse conduction in which the blocked impulse is preceded by prolongation of conduction time relative to the first conducted impulse

In the *typical variety* the increment in conduction time progressively decreases resulting in progressive shortening of the activation interval of the receiving chamber until the blocked impulse occurs. This typical structure is rare but is of importance in recognizing type I exit block.

Most cases of type I block involve *atypical varieties* in which the increment in conduction time varies and it is not necessarily the second impulse of the series which shows the greatest increment (See also *second degree block type II and advanced block*)

**Second degree block type II (Mobitz type II)** Intermittent failure of impulse propagation following a number of conducted impulses showing constant conduction times. The diagnosis of type II block is supported by the finding of a similar conduction interval following the blocked impulse (See also *second degree block type I and advanced block*)

### Short PR syndrome

This is a form of ventricular pre excitation in which the PR interval is shortened to less than

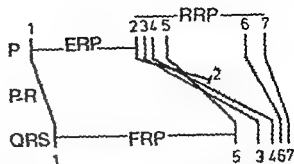


Fig 1 Diagrammatic representation of the various phases of the refractory period of the AV conduction system. P 7 is the first of a series of atrial impulses which is conducted through the AV junction (PR) with the same conduction velocity as P 1. For abbreviations and definitions, see refractory period.

0.12 sec while the QRS complex usually is normal i.e. showing the same configuration as during a normally conducted sinus rhythm. May be associated with re-entrant supraventricular tachycardias. It should be stressed that not all cases showing a short PR interval on the ECG are examples of ventricular pre excitation. Before making such a diagnosis one should ascertain that criteria for ventricular pre excitation are fulfilled (See *Lown-Ganong-Levine syndrome* in *NPT*, *pre excitation* and *Wolff-Parkinson-White pattern and syndrome*).

### Supernormal conduction

Conduction which is less abnormal than would be expected, not faster than normal.

### Supernormal excitability

Unexpected activation resulting from a sub-threshold stimulus. Supernormal excitability is limited to a relatively narrow interval of the cardiac cycle.

### Tachycardia

Three or more consecutive impulses at a rate exceeding 100/min (See also *accelerated rhythm*)

### Third degree or complete block

Complete failure of impulse propagation usually associated with independent and slow activation of the chamber distal to the site of block. In order to diagnose complete block one should ascertain that the opportunity for conduction to occur is present and yet transmission fails. Complete block in one direction does not necessarily imply complete block in the reverse direction (See also *AV dissociation*).

able group of cells showing spontaneous phase 4 depolarization

*Pacemaker ectopic or subsidiary* any pace maker outside the sino atrial (sinus) node

*Pacemaker, primary* the sinus node

Terms like 'latent' and "potential" pace makers refer to inactive (dormant) cells having the property of pacemaking, while subsidiary may refer to both active and latent ectopic pacemakers. A latent pacemaker may be located within the SA node itself

### Parasystole

A rhythm consisting of dual activations of a single cardiac chamber, in which one pacemaker (the parasystolic focus) is protected from being discharged by the other. The latter is usually responsible for the prevailing rhythm

At times two or even more parasystolic rhythms may coexist (*multifocal parasystole*). When the protection intermittently fails, the parasystolic center may be discharged by a penetrating impulse occurring at a critical time interval and parasystole is said to be *intermittent* (See also *entrance block* and *atrioventricular dissociation*)

### Partial block

See *incomplete block*

### Partial re entry

See *re entry*

### Pre excitation

Excitation of part or all of a cardiac chamber earlier than if impulse propagation had occurred over the normal conduction system. The morphology of the excitation wave need not necessarily be different from normal. Anterogradely the ventricles may be pre excited and retrogradely the atria may be pre excited

The term pre excitation can also be applied in cases of artificially induced excitation, wherein mechanical or artificial stimulation occurs prior to or simultaneously with the normally conducted impulse (See also *Wolff Parkinson White pattern and syndrome* and *short PR syndrome*)

**Premature impulse (activation complex or discharge)**

An activation which precedes the expected discharge of the prevailing rhythm. This applies

to extrasystoles, echoes, captures, and manifest activations from a parasystolic pacemaker. Early ventricular activations in atrial fibrillation or flutter should not be called premature since in these arrhythmias prematurity cannot be proven

Premature impulses may occur singly or in pairs (doublets). When three or more are recorded in succession at a rate exceeding 100/min, this is by definition a (brief) *tachycardia*

A premature impulse is usually of ectopic origin

### Quadrigeminy

Defined according to *trigeminy*

### Reciprocal or re entrant impulse

One re entrant movement (see *echo*, *re entry* and *reciprocation*)

### Reciprocation

Continued reentry (circus movement) leading to several consecutive activations of a cardiac chamber (See *re entry*)

### Re entry

The phenomenon in which a cardiac impulse enters a circuit and returns to or toward its area of origin. Re entry may result in one or more activations of the heart or part of it, or it may remain concealed. The latter is evident from the after effect on subsequent impulse formation and/or conduction, and is called *concealed attempted partial or abortive re entry*

### Refractory period

That period in the cardiac cycle during which the conduction system and the myocardium demonstrate no or an altered response to a stimulus. The various phases of the refractory period of the AV conduction system are depicted diagrammatically in Fig 1

**Absolute refractory period (ARP)** That period in the cardiac cycle during which the heart is not excitable. At the cellular level, localized non propagated electrical activity may still be recorded. In a surface or intracavitary recording, the ARP is probably identical to the ERP

**Effective refractory period (ERP)** That period in the cardiac cycle during which an impulse (whether premature or not) fails to conduct (P<sub>1</sub>, P<sub>2</sub> in Fig 1)

**Relative refractory period (RRP)** That interval

tion either regular or irregular or a slow ventricular response due to advanced or complete block. (See also *arrhythmia*)

### Bundle branch block bilateral

Bilateral bundle branch block connotes a conduction disturbance involving both the right bundle branch and the main stem of the left bundle branch or one or both of its fascicles. Like bi and trifascicular block this term serves no special purpose. Instead the site, degree and type of block should be specified. (See also *bi and trifascicular block (LUT)*)

### Chaotic rhythm

This term should be avoided since it is difficult to define chaos. These rhythms are best described as irregular with multiform configuration of the waves. (See *multifocal rhythm*)

### Depolarization

Loss of membrane potential. Since this occurs at a cellular level its use is best restricted to the description of the electrophysiological phenomenon. In clinical electrocardiography when referring to a deflection which represents the electrically active state of the myocardium the term is best replaced by *activation, discharge, excitation* or *impulse*.

### Fibrilla flutter

This term implies a supraventricular arrhythmia with some characteristics of atrial flutter and some of atrial fibrillation. Such records are best classified as atrial fibrillation when the ECG criteria of atrial flutter are not quite satisfied. It should not be mistaken for the alternation of atrial flutter and fibrillation in the same record.

### Hemiblock left anterior

(Left) anterior fascicular block is considered a more appropriate term. (See *fascicular block anterior*)

### Hemiblock left posterior

(Left) posterior fascicular block is considered more appropriate. (See *fascicular block posterior*)

### High degree block

By definition this is still a form of second degree block. However since high degree (high grade) second degree block is a contradiction in terms it

seems more appropriate to classify these conduction disturbances as *advanced (second degree) block*.

### High grade block

See *high degree block*

### Idiofocal tachycardia

This term suggests a focal origin of an enhanced rhythm which may not be true in every case. Furthermore as with the terms *non paroxysmal* and *slow tachycardia* which are sometimes used as synonyms objections may be raised against using the term *tachycardia* at rates below 100/min. The arrhythmia should be characterized as *accelerated rhythm or tachycardia* with further specification according to the site of impulse formation.

### Interference

Rarely has a term created so much disagreement and confusion as interference. Some have used it to indicate the short disturbance of the rhythmic action of one pacemaker by the activity of another (e.g. resetting of a junctional or ventricular pacemaker by a ventricular capture during incomplete AV dissociation) while others have defined interference as the expression of a physiological mechanism namely delay of failure of impulse conduction due to induced normal refractoriness of a conduction pathway or the myocardium (collision of two impulses coming from opposite directions or the same direction).

Since this controversy has not yet been definitively settled if it ever will be it seems best to avoid the term for the time being. There seems to be no reason to indicate emphatically that the activity of a pacemaker is disturbed by a capture as is suggested by the first definition. Only when resetting does not occur may specific phenomenon (protection pasasytyle) be present. On the other hand in analyzing the mechanisms which are responsible for failure of impulse conduction it is convenient to separate an abnormal from a physiological cause. The latter can be indicated by delay or failure of conduction due to refractoriness.

### Intramural conduction disturbance

This term suggests the site of a conduction disturbance within the ventricles causing non-specific widening and/or slurring and notching of the QRS complex. In most cases however the

**Trigeminy**

A repetitive pattern of three relatively closely spaced activations, usually followed by a longer interval. In the most common form of trigeminy, the third impulse is an extrasystole (extrasystolic trigeminy). Rarely, one may be dealing with one sinus impulse followed by two consecutive extrasystoles. The latter is indicated as a doublet.

**Ventriculo atrial (VA) block**

Delay or failure of an impulse to be conducted from the ventricles to the atria (See also *retrograde conduction*)

**Vulnerable period**

A relatively short period in the cycles of atria or ventricles, during which activation results in a repetitive response or fibrillation. The vulnerable phase of the ventricles generally corresponds to the ascending and apical portion of the T wave.

**Wenckebach block**

See *second degree block, type I*

**Wolff Parkinson White (WPW) pattern**

By this is meant pre excitation of the ventricles over an additional and abnormal anatomical AV connection. In such cases excitation over the accessory pathway causes shortening of the PR interval,  $\Delta$  waves and widening of the QRS complex.

Recent knowledge indicates that values for PR interval,  $\Delta$  wave, and QRS width are variable. For instance the PR interval may be longer than 0.12 sec and  $\Delta$  waves may be small and difficult to recognize. Furthermore, the ECG manifestations may be intermittent and the anatomical substrate for reentrant tachycardias may be present although undetectable on the routine surface ECG (See *pre excitation*, *short PR syndrome* and *WPW syndrome*)

**Wolff Parkinson White (WPW) syndrome**

This implies the occurrence of reentrant supraventricular tachycardias in association with the WPW pattern (See also *pre excitation* and *short PR syndrome*)

**LIST OF NON PREFERRED TERMS (NPT)****Accelerated conduction**

Accelerated AV conduction used to be designated whenever a short PR interval ( $< 0.12$  sec) was seen in the absence of other signs of ventric-

ular pre excitation. However true acceleration of conduction has not been demonstrated and recent knowledge indicates that pre excitation of the ventricles via an anatomical connection bypassing the AV nodal delay may result in a short PR interval and normal QRS complex or only a small  $\Delta$  wave. The term "accelerated conduction" is therefore discouraged. Instead, a *short PR syndrome* should be diagnosed whenever circumstantial evidence supports the diagnosis of ventricular pre excitation. In other cases, it seems best to just indicate a *short PR interval* not necessarily implying ventricular pre excitation and thus not identical to the short PR syndrome.

**Antegrade conduction**

See *anterograde conduction*

**Arborization block**

See *intramural conduction disturbance (NPT)*

**Beat**

Use of this term in electrocardiographic nomenclature is inappropriate since it connotes the mechanical event following excitation of a cardiac chamber. Instead, we suggest use of the terms *activation*, *discharge*, *excitation* or *impulse* or more descriptively: *complex*, *deflection* or *wave* (See also *depolarization (NPT)*)

**Bifascicular block**

The term 'bifascicular block' is controversial. In previous terminology the right bundle branch was sometimes referred to as a bundle and some times as a fascicle, this is inconsistent. It is preferable not to consider the right bundle branch as a fascicle. Therefore use of the term 'bifascicular block' for the combination of right bundle branch block plus block in the anterior or posterior fascicle of the left bundle is discouraged. Furthermore block occurring in two fascicles of the left bundle branch cannot usually be differentiated with certainty from main left bundle branch block. Thus even in the latter setting the term bifascicular block serves no special purpose. Instead the site type and degree of block should be specified (See also *trifascicular block (NPT)*)

**Bradyarrhythmia**

The term bradyarrhythmia has been used in various settings to connote slow impulse forma-

## Fine flutterings of the aortic valve as demonstrated by aortic valve echocardiograms

Aortic valve echocardiograms were first recorded by Edler using an excised calf heart. Subsequent studies by Hernberg and associates and by Gramiak and Shah described the typical configuration of the non coronary and right coronary aortic leaflets. Recently Feizi and co workers described this valve in more detail and in their report again noted the boxlike appearance of the aortic leaflets in systole and the central line during diastole. The latter line could be seen as two or three echo signals with hairline separation of 1 mm or less. At the onset of systole the central lines were replaced by two parallel lines lying in close proximity to the aortic root. In their description they mentioned that often a very fine fluttering of the aortic valve echo was seen during systole. However no attempt to ascertain the incidence or conditions under which this fluttering was observed was attempted by this group. We therefore undertook to delineate further the circumstances underlying this phenomenon.

Two hundred fifty consecutive echocardiograms done at the Philadelphia General Hospital non invasive laboratory between March and December 1975 were reviewed. These were obtained using a Unirad ultrasonoscope with a 0.5 inch unfocused transducer emitting 1 000 pulses per second and were recorded on a DR 8 Electronics for Medicine recorder at 50 mm/sec paper speed. Of these 250 echocardiograms reviewed 47 were technically unsuitable and were eliminated.

Those patients with suitable records for study ranged in age from 18 to 76 years (mean  $\pm$  33 years) had a variety of physiological or pathological conditions established by other criteria and included 120 females and 83 males. Methods of obtaining the echocardiograms were after the standard techniques of Feigenbaum. All echocardiograms were performed in the left lateral position with the transducer positioned over the third left intercostal space approximately 3 cm from the sternal edge.

Fine systolic fluttering of the aortic valve was demonstrated in 35 of the 203 recordings, resulting in a prevalence rate for this finding of 17.2 per cent. The distribution of this finding according to normal or disease states is arrayed in Table I. If searched for diligently fluttering may be seen in the majority of normal subjects (four of seven or 57.1 per cent) and otherwise healthy young women in the second or third trimester of pregnancy (11 of 14 subjects or 78.6 per cent). Various disease states leading to hyperdynamic circulation also were associated with this echo observation. These included various anemic (< 9 gm per cent blood hemoglobin concentration) states (eight of 10 patients or 80 per cent), acquired valvular incompetence of the aortic (three of eight patients or 37.5 per cent) or mitral (six of eight patients or 75

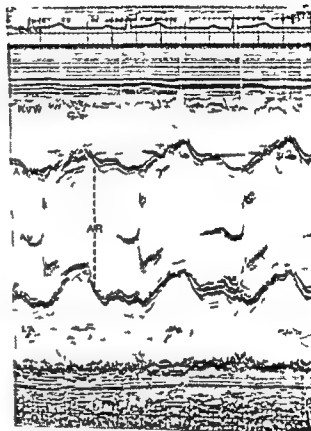


Fig 1 Aortic valve echocardiogram from a patient with non rheumatic aortic regurgitation showing a dilated aortic root and fine systolic fluttering of the aortic leaflets. Abbreviations include ECG = electrocardiogram RVW = right ventricular wall AAW = anterior aortic wall AV = aortic valve leaflets AR = aortic root LA = left atrium.

per cent) valves and in three patients with early and mild labile hypertension. Conversely in 12 patients with rheumatic valvular aortic stenosis and in four patients with calcific aortic stenosis in which aortic valvular excursions were impaired and the circulation was reduced fine systolic fluttering of the aortic leaflets was not seen.

The value of echocardiography as a noninvasive bedside tool in the diagnosis and determination of various cardiac conditions is strengthened with each report of new findings of abnormal motion of any of several cardiac structures. Demon

exact site and extent of the conduction abnormality is not known. Therefore, the non committal term *non specific intraventricular block* is preferred.

#### Lown Ganong Levine syndrome

By this is meant a form of ventricular pre excitation, which is characterized by a short PR interval and normal QRS complex. Generally speaking, eponyms are discouraged, apart from a few historical names. The term 'short PR syndrome' is preferred.

#### Monofascicular block

See *fascicular block anterior and posterior*

#### Myofibrillar block

See *intramural conduction disturbance (LUT)*

#### Non paroxysmal tachycardia

What is meant in most cases is accelerated impulse formation which may or may not occur in paroxysms (bouts or salvos) (See also *idiofocal tachycardia, NPT*)

#### Parietal block

See *intramural conduction disturbance (LUT)*

#### Paroxysmal atrial tachycardia (PAT)

PAT is often diagnosed in cases of supraventricular tachycardia in which the available record does not show paroxysms of tachycardia. Furthermore there is disagreement concerning the mechanism and origin (atrial or AV junctional) of these tachycardias. Most of these arrhythmias are best indicated by the wider concept of (paroxysmal) supraventricular tachycardia.

#### Peri infarction block

See *intramural conduction disturbance (LUT)*

#### Pseudo fusion beat

Superimposition of an artificial pacemaker artifact on a spontaneous P or QRS complex. This indication serves no special purpose and creates confusion.

#### Return extrasystole

The term 'echo' is preferred.

#### Reversed coupling

Resetting of the SA node by an ectopic atrial or retrogradely conducted AV junctional or ventricular impulse. This causes a fixed time relationship between the ectopic impulse and the following sinus discharge. Considering the definition of coupling (see *coupling interval*), however, there seems to be no need for the term 'reversed coupling'.

#### Slow tachycardia

This is a contradiction in terms (See also *idiofocal tachycardia NPT*)

#### Tachyarrhythmia

For some this means a tachycardia with irregular impulse formation or conduction while for others it refers to any tachycardia, regular or irregular (See also *arrhythmia*)

#### Trifascicular block

Use of the term *trifascicular block* for various combinations of block in the anterior and posterior fascicles of the left bundle and in the right bundle branch is discouraged. Instead, the site, type and severity of the conduction defect should be indicated (See also *bifascicular block LUT*)

#### Wandering pacemaker

What is meant is an irregular, multiform (multifocal), supraventricular rhythm with changing P wave morphology and varying PR intervals. The term 'wandering pacemaker' is discouraged since it implies a mechanism which is not readily known (See *multifocal rhythm*)

#### Wedensky effect

The phenomenon in which a subthreshold impulse (stimulus) can result in an effective activation when it is preceded at a given time interval by a maximal or above threshold impulse (stimulus), which itself results in an effective response.

#### Wedensky facilitation

The phenomenon in which during a period of block, a ventricular response causes interruption of the block for variable periods of time.

We wish to express our gratitude to the American College of Cardiology for close cooperation. The authors also acknowledge the help of Miss Gertrude van Eck, Mrs. Manja Helmers and Miss Karin Visser in the preparation of the manuscript.

## Appropriate therapy of hypertension in the elderly

The wisdom of treating hypertension in the elderly has been queried. It has been suggested that anyone over 60 should not be treated.

The first consideration is to define "the elderly" bearing in mind the implications of that term. Certainly over 65 cannot be used as a yardstick. Some few people it is true may be old at 65—but not the majority of a modern Western population. In fact, with increasing health care many of our patients these days remain relatively young and active into their 80s. Certainly it is my rule to assess a person's age by his mental and physical state and never by his years.

The second consideration is to postulate the benefit of treating hypertension in patients of 65 years or over. One has only to consider the folly of a physician not remedying a hypertension of say 200/120 in a man like Sir Winston Churchill when he became Prime Minister of Great Britain in 1940 at the age of 65—or the rashness of a doctor not taking action in the face of a blood pressure of 250/140 in a musician of the caliber of say Rubinstein at the age of 88 to have the answer. The benefits of controlling hypertension at any age and indeed in the older age groups have been clearly demonstrated to be a reduction in the incidence of cerebrovascular accidents, cardiac failure, renal deterioration and neuroretinopathy. Whether a reduction in the incidence of myocardial infarction is achieved as well is open to doubt but it should certainly follow from first principles. As the effect of a stroke may if it is not fatal mean long term incapacity for the patient, then the economics alone are worthy of consideration (it is invariably my practice to lower a very high blood pressure in the face of a stroke usually with apparent benefit).

While it is well known that hypertension is better tolerated in women than in men, never the less the dangers over the age of 65 appear to be the same.

It is also common knowledge that hypertension is self feeding by reason of renal damage and therefore to check the rise in blood pressure may be of positive benefit to a patient even if the underlying causation remain untreated. It follows from this last that extensive investigation is not necessarily indicated in the elderly but that benefit may nevertheless accrue from control of the blood pressure.

From the above it may be sensed that in the older groups of patients the management and investigation of hypertension should be flexible and tailored to the individual patient. Included in the assessment of the patient must be his or her personality. This is important because by undue investigation and therapy in a particularly anxious person the physician may do more harm than good—and many older patients are often anxious either due to slower comprehension or a sense of isolation which may be threatened or real. Treatment in any case in older patients must be kept as simple as possible.

Treatment is not helped by the fact that many cases of hypertension are discovered casually when the patient is seen for some other unrelated complaint. Such patients can easily come to resent what they may regard as undue interference

with their lives especially if the treatment proffered makes them feel ill whereas they probably felt very well before!

The physician will certainly find that whereas some patients will cooperate enthusiastically in proposed regimes others will not. In many cases the physician may well have to accept a compromise far from the ideal and hold a watching brief rather than put the patient off altogether to the latter's peril.

Having said this when a case of hypertension is discovered in a patient in his sixties or over it is my practice to give a brief physical examination. This will include the abdomen (including the femoral arteries) for signs of tumor e.g. enlarged kidney hypernephroma etc. the heart for signs of enlargement aortic disease etc. the lungs for signs of cardiac failure the lower limbs for edema and the fundi for arterial assessment. An ECG is not performed. The urine is checked for albumen sugar and blood—and microscopy and culture are undertaken when indicated. The blood is checked for hemoglobin urea lipids and cholesterol—and sugar if there is glycosuria. (The lipids and cholesterol are estimated not only for the physician's interest but because I see no reason why the progressive effects of hyperlipidemia and hypercholesterolemia should necessarily go unchecked at whatever age they are discovered. They may indeed be reversible.)

Next what level of blood pressure is taken as indicating the need for therapy? I think that any blood pressure of 160/100 worthy of observation in the late 50s or 60s and in such cases I have them reviewed by my practice nurse at 6 monthly or annual intervals. In the 70s I am similarly prepared to review blood pressures of 170/110—and in the 80s blood pressures of 180/120/115. With blood pressures above these levels I institute gentle treatment and control certainly paying as much attention to an undue elevation of the systolic pressure as one in the diastolic. In the 90-year olds I feel we are dealing very much with special cases and each will be managed on its individual merits. (In B. The diastolic pressures given here refer to the fourth phase i.e. muffling of sounds and not the fifth phase or resumption of sounds.)

The first therapeutic measures will be to correct if possible any etiological factors such as urinary tract infection obesity etc. At the same time the blood pressure will be observed at short intervals of a week or two when it is found in some cases that the pressure settles and no therapy is required.

If drug therapy is necessary then it is my practice to proceed cautiously. This holds for people in any age group because patients vary so much in their response to the potent drugs which we nowadays exhibit. For instance some patients have a magnificent diuresis with 5 mgm of furosemide—and will be put into a state of collapse by the usual dose of 40 mgm! Similarly a small dose of methyldopa can produce a devastating fall of blood pressure in some people while having little effect in others. In older patients such untoward effects may be even more pronounced because of arterial hardening and the slowing of the vasoconstrictor reflexes. Certainly the danger of postural hypotension must be constantly borne in mind.





Fig 2 Fine systolic fluttering in a patient with non rheumatic mitral regurgitation. The characteristics and morphology of fluttering are similar to that in Fig 1. Abbreviations are the same as in Fig 1.

strations of abnormal aortic leaflet or aortic vascular motion have now been documented in several settings including valvular aortic stenosis, bicuspid aortic valves, asymmetrical septal hypertrophy, flail leaflets in aortic valve endocarditis, and dissection of the ascending aorta. Less attention has been directed toward the more subtle findings found in apparently normal valves. Several workers including Fein and colleagues, Gramiak and Shah, and Winsberg<sup>1</sup> have contended that fine systolic oscillations of the aortic valve cusps may be seen in normal leaflets if searched for with sufficient effort. The frequency of this finding in normal subjects or its presence in other pathological or physiological conditions was not mentioned. The present report suggests its broad occurrence not only in normal controls but in a variety of other settings including pregnancy, anemia, aortic and mitral valvular regurgitation and labile hypertension. While it is as yet premature to suggest an underlying causal mechanism, the latter conditions are in many instances characterized by hyperdynamic circulations. The fine systolic flutterings may represent an effect of local turbulence on pliable aortic valve leaflets as induced by an altered hemodynamic state. Conversely, the absence of systolic oscillations in valvular aortic stenosis, in spite of equal local turbulence in blood flow, may be explained by the thickening of the valve leaflets with resulting restrictions in leaflet movement. The finding of high frequency fluttering of the aortic valve leaflets in

Table 1 Echocardiograms demonstrating fine systolic flutter\*

| Condition  | Number demonstrated flutter | Number studied |
|--|-----------------------------|----------------|
| Normal subjects with functional or benign systolic murmurs | 4                           | 7              |
| Pregnancy  | 11                          | 14             |
| Anemia   | 8                           | 12             |
| Aortic regurgitation                                       | 3                           | 8              |
| Non rheumatic mitral regurgitation                         | 6                           | 8              |
| Labile hypertension  | 3                           | 3              |
| Valvular aortic stenosis                                   | 0                           | 16             |
| Totals   | 35                          | 68             |

A total of 250 echocardiograms were reviewed of which 203 were used in the study. Of these 35 demonstrated fine systolic flutter.

the presence of an outflow type murmur (and in the absence of aortic regurgitation) would suggest a pliable normal valve and may therefore provide a useful aid in distinguishing a functional murmur from one resulting from organic valve stenosis.

Eduard R. Pinto MD  
Prabodh M. Damani MD  
Cora N. Sternberg MD  
A. James Liedtke MD  
Milton S. Hershey Medical Center  
Section of Cardiology  
Pennsylvania State University  
Hershey Pa 17033

#### REFERENCES

1. Edler I. *Ultrasonocardiology in ultrasound as a diagnostic and surgical tool*. Edited by D. Gordon. Baltimore 1964. The Williams & Wilkins Company p 124.
2. Hernberg J, Weiss H, and Keegan A. The ultrasonic recording of aortic valve motion. *Radiology* 94: 361, 1970.
3. Gramiak R, and Shah P M. Echocardiography of the normal and diseased aortic valve. *Radiology* 96: 1, 1970.
4. Fein O, Symons C, and Yacoub M. Echocardiography of the aortic valve. *Br Heart J* 36: 341, 1974.
5. Feigenbaum H. *The echocardiographic examination in Echocardiography*. Philadelphia 1972. Lea & Febiger Publishers p 25.
6. Feigenbaum H. *Aortic valve in Echocardiography*. Philadelphia 1972. Lea & Febiger Publishers p 73.
7. Nanda M C, Gramiak R, Manning J, Mahoney E B, and Dewese J A. Echocardiographic recognition of congenital bicuspid aortic valve. *Circulation* 49: 870, 1974.
8. Feigenbaum H. Clinical applications of echocardiography. *Progr Cardiovasc Dis* 14: 531, 1972.
9. Wray T M. The variable echocardiographic features of aortic valve endocarditis. *Circulation* 52: 658, 1975.
10. Mootart R W, Spangler R D, and Blount S. Echocardiography in aortic root dissection and dilation. *Am J Cardiol* 36: 11, 1975.
11. Winsberg F. *Aortic valve in Cardiac ultrasound*. Edited by R. Gramiak and R C. Wsag. Saint Louis 1975. The C V Mosby Company p 74.

cians using verapamil for its cardiotonic or anti hypertensive effects.

Allan Davidson MD

Ian McMurtry PhD

JT Reeves MD

CVP Research Laboratory

University of Colorado

Medical Center

4200 East Ninth Ave

Denver Colo 80262

## REFERENCES

1. Kinkler D Verapamil in cardiology *Europ J Cardiol* 23 1974
2. Nayler W H and Kinkler D Verapamil and the myocardium *Postgrad Med J* 50 441 1974
3. Bohr D F Vascular smooth muscle updated *Circ Res* 33 665 1973
4. McMurtry I F Davidson A B Reeves J T and Grover R F Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs *Circ Res* 38 99 19 6
5. Tucker A McMurtry I F Grover R F and Reeves J T Attenuation of hypoxic pulmonary vasoconstriction by verapamil in intact dogs *Proc Soc Exp Biol Med* 151 611 19 6
6. Abraham A S Kay J M Cole R B and Pincock A C Haemodynamic and pathological study of the effect of chronic hypoxia and subsequent recovery of the heart and pulmonary vasculature of the rat *Cardiovasc Res* 5 95 1971

Table I

|            | Low<br>altitude<br>saline | Low<br>altitude<br>verapamil | High<br>altitude<br>saline | High<br>altitude<br>verapamil |
|------------|---------------------------|------------------------------|----------------------------|-------------------------------|
| RV/T ratio | 0.23<br>± 0.01            | 0.22<br>± 0.01               | 0.37<br>± 0.01†            | 0.30<br>± 0.01 †              |
| No rats    | 4                         | 5                            | 6                          | 11                            |

† significantly different from high altitude saline group (P < 0.01)

‡ significantly different from either low altitude group (P < 0.01)

of hypoxic pulmonary hypertension was assessed by measuring the degree of right ventricular hypertrophy using the ratio of the weight of the free wall of the right ventricle to the total ventricular weight.

Treatment with verapamil did not affect left ventricular weight nor did it affect the hematocrit (low altitude 45 per cent high altitude 63 per cent) suggesting that the hypoxic stimulus was the same in verapamil and saline treated groups. The values shown indicate that saline treated high altitude rats developed more right ventricular hypertrophy than verapamil treated animals. The smaller degree of right ventricular hypertrophy in high altitude rats treated with verapamil was presumably due to a lower level of hypoxic pulmonary hypertension. This finding is consistent with the observation that verapamil inhibits the pulmonary pressor response to acute alveolar hypoxia. The possibility of similar hemodynamic effects in man should be considered by physi-

## Of why the two heart pumps are anatomically united to form one heart

The heart is composed of two separate pumps which are separated circulatorily by the pulmonary vascular system and the systemic vascular system. As indicated previously the two separate pumps must be properly synchronized and integrated in their pumping of blood or the distribution of blood volume throughout the entire circulation would be seriously disturbed and either acute pulmonary congestion with acute pulmonary edema would result or the pulmonary vessels would become emptied of blood. To appreciate this fully a previous publication should be studied closely.

It is interesting to speculate why there is a two pump cardiac system and why the two pumps are closely anatomically intertwined to form one anatomic heart. This arrangement is an important efficient and desirable one. For example were the right and left sides of the heart—the two pumps—completely separated pulmonary congestion would suddenly occur if supraventricular or ventricular tachycardia developed in the independent and anatomically separate right heart while the left atrium and left ventricle continued to contract 0 or so times per minute. More blood would be ejected into the pulmonary vessels by the right pump than would be removed from these vessels by the left pump. Were the left atrium or ventricle to develop supraventricular or

ventricular tachycardia more blood would be removed from the pulmonary vessels than would be pumped into them by the separate right heart pump and the pulmonary vessels would become dry or essentially empty. These states would result in serious and acute circulatory disturbances and even death of the individual. On the other hand with the right and left pumps joined anatomically as they are both pumps respond essentially simultaneously to tachycardias or extra systole. Neither side of the heart can fibrillate or contract separately. This arrangement usually (I can think of exceptions) assures a well balanced circulation which is essential for a good circulatory state as indicated elsewhere even in the presence of arrhythmias which are initiated in either the right or left pump.

George E Burch MD

Tulane University School of Medicine

and Charity Hospital of Louisiana

New Orleans La

## REFERENCES

1. Burch G E A primer of congestive heart failure Springfield Ill 1954 Charles C Thomas Publisher
2. Burch G E Congestive heart failure is not due to low cardiac output per se *AM HEART J* 94 769 19 7

It is my practice to prescribe initially small doses of a mild diuretic—usually a thiazide (but bearing in mind these drugs diabetogenic qualities). The patient's own observations as to effect will be carefully listened to and considered as well as recording the response of the blood pressure and apex rate. If necessary the dose can be cautiously increased. If the blood pressure still remains at a higher level than is desired it is my practice to add on small doses of either a beta blocker (propranolol) or methyldopa or clonidine or rarely bethanidine or guanethidine.

Again it must be emphasized that *with older patients caution must be the keynote of therapy* and small doses must be used initially with frequent assessments made of the response obtained—say every three to seven days. These assessments will be made by the practice nurse, the doctor advising with regard to dosage etc. Self monitoring by the patient is probably by and large unsatisfactory but may be possible with some.

Once satisfactory control has been achieved it is essential to monitor the patient from time to time—say at three or six monthly intervals. As the years go by the older patients' blood pressure will be found to drop if therapy has been maintained—presumably due to progressive myocardial degeneration. In such cases it will be essential to reduce the dosage of the treatment. (The onset of Addison's Disease will also be discovered in the elderly—particularly if it is borne in mind and looked for.) Those patients taking methyldopa should have a periodical Coombs test and hemoglobin estimation. The urine especially of those patients taking thiazides should be periodically checked for sugar and the electrolytes of any patient taking a diuretic should be borne in mind as with the blood urea and uric acid. Infection and warm weather may dramatically lower the blood pressure, especially in the elderly and this must not be lost sight of. Depression is a side effect of both beta blockers, methyldopa, bethanidine and guanethidine and should be looked for. (I no longer use the rauwolfia alkaloids for this reason.) Clonidine may cause mental disturbance. Impotence with all these drugs may be a problem. The dangers of the beta blockers in asthma, diabetes and cardiac failure must not be overlooked nor the fact that there is some evidence that they are contraindicated in generalized psoriasis and systemic lupus erythematosus. The onset of a paroxysmal heart block may pose problems only soluble by the use of a pacemaker.

It should be re-emphasized that the *drug regime should be kept as simple as possible* so that it will not only be understood but taken properly by the patient. There is

probably a place here for some of the combined preparations which many of us are normally loath to prescribe.

In conclusion it may be said that hypertension is a disease *par excellence* of the elderly. Over the age of 65 the systolic blood pressure can climb dramatically. The treatment of hypertension in such elderly patients is rewarding both in terms of health and economics *provided that it is done with due care and caution*. This treatment may be undertaken relatively simply and at comparatively small cost.

My thanks are due to Dr H G Mather MD FRCP of Bristol for his help and advice with the preparation of this annotation.

D T C Barlow MB BS FRCP Order of St John  
General Practitioner  
North Devon England  
110 Boutport Street  
Barnstaple EX31 1TB  
England

# REFERENCES

- 1 Jackson G, Piercianowski T A, Mahon W and Condon J. Inappropriate antihypertensive therapy in the elderly. *Lancet* 2 1317 1976.
- 2 Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213 1143 1970.
- 3 Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202 1028 1967.
- 4 Kanel W B and Dawber T R. Hypertension as an ingredient of a cardiovascular risk profile. *Br J Hosp Med* 11 508 1974.
- 5 Barham Carter A. Hypotensive therapy in stroke survivors. *Lancet* 1 485 1970.
- 6 Flora G C, Baker A B, Lowenson R and Klassen A C. Atherosclerosis in males and females. *Circulation* 38 859 1968.
- 7 Gresham G A. Is atheroma a reversible lesion? *Atherosclerosis* 23 379 1976.
- 8 Leshman A W D and Sandler G. Hastening the control of blood pressure by guanethidine. *Lancet* 1 668 1965.
- 9 Burns Cox C J, Rees J, Russell Wilson R S E. Pilot study of home measurement of blood pressure by hypertensive patients. *Br Med J* 3 80 1975.
- 10 Parsons H L. Personal Communication. Guy's Hospital London 1977.
- 11 Hamilton M, Pickering G W, Roberts J A F and Sowry G S C. The aetiology of essential hypertension. I. The arterial pressure in the general population. *Clin Sci* 13 11 1954.

## Pulmonary vascular effects of verapamil

Verapamil, a synthetic compound related to papaverine, is currently under study as an anti-arrhythmic and antihypertensive agent. It depresses transmembrane calcium influx in cardiac and vascular smooth muscle, thereby resulting in membrane stabilization. We have shown that verapamil inhibits the pulmonary pressor response to acute alveolar hypoxia in isolated rat lungs and anesthetized dogs. We wondered

whether verapamil would depress the development of pulmonary hypertension during chronic alveolar hypoxia. Therefore we exposed 250 gram male Sprague Dawley rats to local altitude (1 600 M) or to a simulated high altitude (5 500 M) in a hypobaric chamber for 20 days. Half the rats at each altitude received 4 mg verapamil in 0.5 cc saline intraperitoneally twice a day and the other half received only saline. The degree

alternating with re-entrant extrasystoles (manifested and concealed)

Shunji Kinoshita MD  
Second Department of Medicine  
Hokkaido University School of Medicine  
Sapporo Japan

#### REFERENCES

- 1 Kinoshita S. Concealed ventricular extrasystoles due to interference and due to exit block. *Circulation* 52:230 1975
- 2 Kinoshita S. Wenckebach phenomenon of entrance block in intermittent ventricular parasystole. *Chest* 66:530 1974
- 3 Kinoshita S. Intermittent parasystole originating in the re-entrant path of ventricular extrasystoles. *Chest* 72:901 1977

#### Reply

##### To the Editor

I appreciate and welcome Dr. Kinoshita's interest and his suggestions regarding the phenomena observed in my case of intermittent parasystole with concealed bigeminy.

Dr. Kinoshita has obviously shown innovative expertise in the complex rarer manifestations of intermittent parasystole and concealed bigeminy as exemplified by both his and my bibliography.

I, myself, was perplexed to explain the successive cycle length shortening in each parasystolic series and proposed several mechanisms in my discussion. Dr. Kinoshita has demonstrated in previous articles (his references 1 to 3) that there is often a relative refractory period late in an intermittent parasystolic cycle length and that either complex alterations in resetting or re-entrant extrasystoles can result because of entrance or exit block conduction delay. His proposed mechanism of re-entry however would explain only isolated abbreviation of terminal cycle lengths. As shown in my table, cycle lengths tended to gradually shorten during a parasystolic series although some even lengthened including the last cycle.

If each parasystolic cycle length were divided into two parts, with one interval being from parasystolic to conducted beat and the other interval from conducted to parasystolic beat and a curve were constructed plotting these intervals against each other, one would see a reciprocal relationship with a slope of identity. Only 4 points out of 60 deviated from this curve. These points all demonstrated short coupling intervals (0.46 to 0.51 sec) to preceding conducted beats relatively long intervals between parasystolic and the following conducted beats (1.18 to 1.49 sec) approaching the end of the parasystolic refractory period (1.22 sec) and were also terminal cycle lengths in a parasystolic series. These beats could well be re-entrant, as suggested by Dr. Kinoshita.

Levy and Kern have recently described two cases which demonstrated rhythm sequences and interval changes identical to those of my case report and have formulated an entirely different mechanism which excludes intermittent parasystole. They proposed re-entry extrasystolic loops with various sites of block to explain both their and my observations of even number sequences of conducted beats between ectopic series and single conducted beats during ectopic series. The progressive shortening of both coupling intervals and

interectopic intervals during a bigeminal sequence was thought secondary to a positive feedback system in a re-entry loop rather than to an intermittent parasystolic mechanism. This re-entry formulation could possibly explain the phenomena in my case and is essentially a more complicated modification of Dr. Kinoshita's suggestions.

Paul R. Lightfoot MD  
Department of Cardiology  
Kaiser Permanente Medical Center  
9885 Sierra Ave  
Fontana, Calif 92335

#### REFERENCE

- 1 Levy M, N. Kern N, and Eisenstein I. A subvariant of concealed bigeminy. *J Electrocardiol* 10:225 1977

#### More on effectiveness of the CCU

##### To the Editor

In a recent annotation Dr. Lindholm and colleagues write that no well-controlled study has as yet been reported about the effectiveness of coronary care units (CCU) in reducing the mortality of acute myocardial infarction although CCUs offer a certain marginal gain as some patients are resuscitated who would otherwise have died. Regarding this latter affirmation we feel that what is marginal in mortality rate perhaps is not so for the patient and for his family. Moreover it must be stressed that results of all present medical activities are disappointing as far as the mortality rate is concerned. This does not hinder us from treating patients. Medical activity in most cases has always reached individual results.

Dr. Lindholm and associates also write that the results of CCUs could be achieved in many other diseases provided that the patients were (or could be) as carefully supervised as in CCUs. It is desirable that this be done but we doubt that results of CCUs could be obtained. Results of CCUs in acute myocardial infarction depend indeed on saving hearts which anatomically are too good to die. It seems there are not many similar situations in the pathology of other organs.

Instead we completely agree with Dr. Lindholm and co-workers when they affirm that CCUs must not be too numerous for this WHO has given appropriate instructions. We add also that CCUs must not be expensive. CCUs essentially prevent deaths from arrhythmias for this ECG monitoring is of foremost importance. Only ECG monitors and defibrillators are fundamental, and well trained attendants and dedicated doctors and nurses remain imperative. A CCU with only these essential elements perhaps is no more a CCU. But too many CCUs are only a useless exhibition of electromedical instrumentation.

Pierfilippo Fazzini  
Francesco Marchi  
Paolo Pucci  
Department of Cardiology  
Arcispedale di S. Maria Nuova  
Florence Italy

#### REFERENCES

- 1 Lindholm J, Fabritius-Bjerre N, Arisvold R, and Kjærlund J. Coronary care units. *AM HEART J* 91:673 1976

# Parasystole and re entry

To the Editor

I read with much interest the report by Dr Lightfoot on intermittent ventricular parasystole with concealed extrasystolic bigeminy (THIS JOURNAL 93 229 1977) I agree with Dr Lightfoot on all of the explanations suggested in his report except for the following finding. His case showed that the last ectopic cycle length in each parasystolic series was usually the shortest in the series. For this finding I would like to offer an explanation different from that suggested by Dr Lightfoot. The mechanism suggested by me is illustrated in Fig 1 in which the early portion of the bottom strip of panel B shown in Lightfoot's Fig 2 is diagrammatically represented.

As pointed out by him the last interectopic interval  $E_1E$  in the first parasystolic series of Fig 1 here is the shortest in the series which measures a period of 168 (All of the time intervals in this letter are expressed in hundredths of a second.) This last interectopic interval  $E_1E$  is definitely shorter than either of the preceding interectopic intervals  $E_1E_1$  and  $E_1E_1$ . Dr Lightfoot considered that the ectopic beats including the last ectopic beat in each series were all parasystolic beats. On this assumption he explained that the refractory period of the parasystolic focus's protection from conducted sinus beats was a period of 122 or 124 and that the parasystolic rate tended to slightly accelerate during each series owing to a warming up of the ectopic pacemaker.

An alternative explanation for the above finding is illustrated by the diagram in Fig 1. The interectopic interval  $E_1E_1$  (i.e. a period of 179) is not shorter than its preceding interectopic interval  $E_1E_1$  (i.e. a period of 177) namely, acceleration of the parasystolic rate is not seen here. The conducted sinus impulses preceding these ectopic beats i.e. the impulses  $S_1$ ,  $S_2$  and  $S_3$  fall in the refractory period of the ventricular ectopic (V E) junction and therefore the ectopic focus is protected from these impulses. However the V E refractory period here is somewhat shorter than that suggested by Dr Lightfoot so that the conducted sinus impulse  $S_4$  preceding the last ectopic beat in the series falls shortly after the V E refractory period. Thus after marked

delay the sinus impulse  $S_4$  reaches and discharges the ectopic focus with resetting of the parasystolic rhythm. After that the impulse  $S_4$  becomes a re-entrant extrasystole  $E_1$ . Namely the ectopic beat  $E_1$  is not a parasystolic beat. Therefore the last interectopic interval in an ectopic series is the shortest in the series not because the parasystolic rate tends to accelerate but because the last ectopic beat in the series is a re-entrant extrasystole. Shaded areas in the diagram represent the refractory period.

On the other hand the conducted sinus impulse  $S_5$  subsequent to the re-entrant extrasystole  $E_1$  falls long after the V E refractory period and therefore it reaches the ectopic focus after not enough delay to become a re-entrant extrasystole. In other words it becomes a concealed extrasystole due to interference so termed by Kinoshita. The conducted sinus impulses  $S_5$  and  $S_6$  fail to disturb the parasystolic rhythm because they interfere with the parasystolic impulses ( $E_1$ ) and ( $E_2$ ) respectively within the V E junction and cannot reach the ectopic focus as suggested in my previous report. The sinus impulse  $S_7$  and the parasystolic impulse  $E_2$  interfere within the ventricles indicating a ventricular fusion beat.

Such a marked conduction delay within the V E junction suggested in this letter was also indicated in my recently reported cases of intermittent ventricular parasystole.<sup>1,2</sup> In one of these cases when a sinus impulse fell shortly after the V E refractory period it reached the parasystolic focus after marked delay and thereafter became a re-entrant extrasystole showing the same configuration as that of the parasystolic beats. Warming up of the ectopic pacemaker i.e. acceleration of the ectopic rate usually occurs after the ectopic focus is repeatedly discharged at a markedly rapid rate in comparison with the basic rate of the ectopic pacemaker. In intermittent parasystole however the parasystolic pacemaker cannot be repeatedly discharged at such a rapid rate because the refractory period of the parasystolic focus's protection is markedly prolonged. Thus I think that the case of Dr Lightfoot may probably show intermittent parasystole.

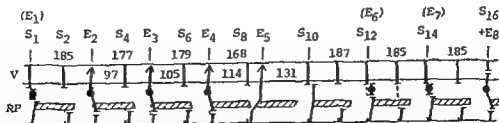


Fig 1 Diagram illustrating intermittent ventricular parasystole alternating with re-entrant extrasystoles (manifested and concealed). Time intervals are expressed in hundredths of a second. Shaded areas represent the refractory period. Intraventricular conduction of the sinus (or ectopic) impulse leading to the ventricular ectopic junction is indicated by dashed lines.  $S$  = sinus impulse conducted to the ventricles.  $E$  and ( $E$ ) = ectopic beat and concealed ectopic impulse respectively.  $S + E$  = ventricular fusion beat.  $V$  = ventricles.  $RP$  = re-entrant path containing the ventricular ectopic junction, the parasystolic focus and the ectopic ventricular junction.

alternating with re-entrant extrasystoles (manifested and concealed).

Shuji Kinoshita M.D.  
Second Department of Medicine  
Hokkaido University School of Medicine  
Sapporo Japan

## REFERENCES

- 1 Kinoshita S. Concealed ventricular extrasystoles due to interference and due to exit block. *Circulation* 52:730 1975
- 2 Kinoshita S. Wenckebach phenomenon of entrance block in intermittent ventricular parasystole. *Chest* 66:570 1974
- 3 Kinoshita S. Intermittent parasystole originating in the re-entrant path of ventricular extrasystoles. *Chest* 72:701 1977

## Reply

## To the Editor

I appreciate and welcome Dr. Kinoshita's interest and his suggestions regarding the phenomena observed in my case of intermittent parasystole with concealed bigeminy.

Dr. Kinoshita has obviously shown innovative expertise in the complex rarer manifestations of intermittent parasystole and concealed bigeminy as exemplified by both his and my bibliography.

I myself was perplexed to explain the successive cycle length shortening in each parasystolic series and proposed several mechanisms in my discussion. Dr. Kinoshita has demonstrated in previous articles (his references 1 to 3) that there is often a relative refractory period late in an intermittent parasystolic cycle length and that either complex alterations in resetting or re-entrant extrasystoles can result because of entrance or exit block conduction delay. His proposed mechanism of re-entry however would explain only isolated abbreviation of terminal cycle lengths. As shown in my table cycle lengths tended to gradually shorten during a parasystolic series although some even lengthened including the last cycle.

If each parasystolic cycle length were divided into two parts with one interval being from parasystolic to conducted beat and the other interval from conducted to parasystolic beat, and a curve were constructed plotting these intervals against each other one would see a reciprocal relation hip with a slope of identity. Only 4 points out of 10 deviated from this curve. These points all demonstrated short coupling intervals (0.46 to 0.51 sec.) to preceding conducted beats, relatively long intervals between parasystolic and the following conducted beats (1.18 to 1.20 sec.) approaching the end of the parasystolic refractory period (1.27 sec.) and were also terminal cycle lengths in a parasystolic series. These beats could well be re-entrant as suggested by Dr. Kinoshita.

Levy and Kern have recently described two cases which demonstrated rhythm sequences and interval changes identical to those of my case report and have formulated an entirely different mechanism which excludes intermittent parasystole. They proposed re-entry extrasystolic loops with various sites of block to explain both their and my observations of even number sequences of conducted beats between ectopic series and single conducted beats during ectopic series. The progressive shortening of both coupling intervals and

interectopic intervals during a bigeminal sequence was thought secondary to a positive feedback system in a re-entry loop rather than to an intermittent parasystolic mechanism. This re-entry formulation could possibly explain the phenomena in my case and is essentially a more complicated modification of Dr. Kinoshita's suggestions.

Paul R. Lightfoot M.D.  
Department of Cardiology  
Kaiser Permanente Medical Center  
9985 Sierra Ave  
Fontana Calif 92335

## REFERENCE

- 1 Levy M N, Kern N and Eisenstein I. A subvariant of concealed bigeminy. *J Electrocardiol* 10:220 1977

## More on effectiveness of the CCU

## To the Editor

In a recent annotation Dr. Lindholm and colleagues write that no well-controlled study has as yet been reported about the effectiveness of coronary care units (CCU) in reducing the mortality of acute myocardial infarction although CCUs offer a certain marginal gain as some patients are resuscitated, who would otherwise have died. Regarding this latter affirmation we feel that what is marginal in mortality rate perhaps is not so for the patient and for his family. Moreover it must be stressed that results of all present medical activities are disappointing as far as the mortality rate is concerned. This does not hinder us from treating patients: medical activity in most cases has always reached individual results.

Dr. Lindholm and associates also write that the results of CCUs could be achieved in many other diseases provided that the patients were (or could be) as carefully supervised as in CCUs. It is desirable that this be done but we doubt that results of CCUs could be obtained. Results of CCUs in acute myocardial infarction depend indeed on saving hearts which anatomically are too good to die. It seems there are not many similar situations in the pathology of other organs.

Instead we completely agree with Dr. Lindholm and co-workers when they affirm that CCUs must not be too numerous for this WHO has given appropriate instructions. We add also that CCUs must not be expensive. CCUs essentially prevent deaths from arrhythmias for this ECG monitoring is of foremost importance. Only ECG monitors and defibrillators are fundamental, and "well trained attendants and dedicated doctors and nurses remain imperative. A CCU with only these essential elements perhaps is no more a CCU. But too many CCUs are only a useless exhibition of electromedical instrumentation.

Pierfilippo Fa-zini  
Francesco Marchi  
Paolo Pucci  
Department of Cardiology  
Arcispedale di S. Maria Nuova  
Florence Italy

## REFERENCES

- 1 Lindholm J, Fabricius-Bjerre N, Aastad, K. and Kjaerulf J. Coronary care units. *AM HEART J* 91:673 1976

# Parasystole and re entry

To the Editor

I read with much interest the report by Dr Lightfoot on intermittent ventricular parasystole with concealed extrasystolic bigeminy (THIS JOURNAL 93 229 1977) I agree with Dr Lightfoot on all of the explanations suggested in his report except for the following finding. His case showed that the last ectopic cycle length in each parasystolic series was usually the shortest in the series. For this finding I would like to offer an explanation different from that suggested by Dr Lightfoot. The mechanism suggested by me is illustrated in Fig 1 in which the early portion of the bottom strip of panel B shown in Lightfoot's Fig 1 is diagrammatically represented.

As pointed out by him the last interectopic interval  $E_1E_2$  in the first parasystolic series of Fig 1 here is the shortest in the series which measures a period of 168 (All of the time intervals in this letter are expressed in hundredths of a second). This last interectopic interval  $E_1E_2$  is definitely shorter than either of the preceding interectopic intervals  $E_1E_2$  and  $E_2E_3$ . Dr Lightfoot considered that the ectopic beats including the last ectopic beat in each series were all parasystolic beats. On this assumption he explained that the refractory period of the parasystolic focus protection from conducted sinus beats was a period of 122 or 124 and that the parasystolic rate tended to slightly accelerate during each series owing to a warming up of the ectopic pacemaker.

An alternative explanation for the above finding is illustrated by the diagram in Fig 1. The interectopic interval  $E_1E_2$  (ie a period of 179) is not shorter than its preceding interectopic interval  $E_2E_3$  (ie a period of 177) namely acceleration of the parasystolic rate is not seen here. The conducted sinus impulses preceding these ectopic beats ie the impulses  $S_1$ ,  $S_2$  and  $S_3$  fall in the refractory period of the ventricular ectopic (V E) junction and therefore the ectopic focus is protected from these impulses. However the V E refractory period here is somewhat shorter than that suggested by Dr Lightfoot so that the conducted sinus impulse  $S_4$  preceding the last ectopic beat in the series falls shortly after the V E refractory period. Thus after marked

delay the sinus impulse  $S_4$  reaches and discharges the ectopic focus with resetting of the parasystolic rhythm. After that the impulse  $S_4$  becomes a re-entrant extrasystole  $E_4$ . Namely the ectopic beat  $E_4$  is not a parasystolic beat. Therefore the last interectopic interval in an ectopic series is the shortest in the series not because the parasystolic rate tends to accelerate but because the last ectopic beat in the series is a re-entrant extrasystole. Shaded areas in the diagram represent the refractory period.

On the other hand the conducted sinus impulse  $S_5$  subsequent to the re-entrant extrasystole  $E_4$  falls long after the V E refractory period and therefore it reaches the ectopic focus after not enough delay to become a re-entrant extrasystole. In other words it becomes a concealed extrasystole due to interference so termed by Kinoshita. The conducted sinus impulses  $S_5$  and  $S_6$  fail to disturb the parasystolic rhythm because they interfere with the parasystolic impulses ( $E_5$ ) ( $E_6$ ) and ( $E_7$ ) respectively within the V E junction and cannot reach the ectopic focus as suggested in my previous report. The sinus impulse  $S_7$  and the parasystolic impulse  $E_7$  interfere within the ventricle, indicating a ventricular fusion beat.

Such a marked conduction delay within the V E junction as suggested in this letter was also indicated in my recently reported cases of intermittent ventricular parasystole.<sup>1,2</sup> In one of these cases when a sinus impulse fell shortly after the V E refractory period it reached the parasystolic focus after marked delay and thereafter became a re-entrant extrasystole showing the same configuration as that of the parasystolic beats. Warming up of the ectopic pacemaker ie acceleration of the ectopic rate usually occurs after the ectopic focus is repeatedly discharged at a markedly rapid rate in comparison with the basic rate of the ectopic pacemaker. In intermittent parasystole however the parasystolic pacemaker cannot be repeatedly discharged at such a rapid rate because the refractory period of the parasystolic focus protection is markedly prolonged. Thus I think that the case of Dr Lightfoot may probably show intermittent parasystole

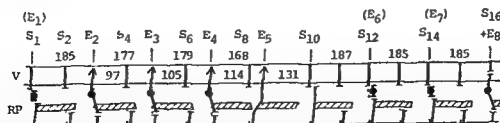


Fig 1 Diagram illustrating intermittent ventricular parasystole alternating with re-entrant extrasystoles (manifested and concealed). Time intervals are expressed in hundredths of a second. Shaded areas represent the refractory period. Intraventricular conduction of the sinus (or ectopic) impulse leading to the ventricular ectopic junction is indicated by dashed lines.  $S$  = sinus impulse conducted to the ventricles.  $E$  and  $E$  = ectopic beat and concealed ectopic impulse respectively.  $S + E$  = ventricular fusion beat.  $V$  = ventricles.  $RP$  = re-entrant path containing the ventricular ectopic junction, the parasystolic focus and the ectopic ventricular junction.

## Book reviews

**Non invasive Clinical Measurement** Edited by David Taylor and Joan Whamond Baltimore 1977 University Park Press 205 pages Price \$39 0

This book is edited by Taylor and Whamond of the Department of Applied Physiology and Surgical Sciences of the Royal College of Surgeons of England. The book consists of several papers gathered into three sections namely blood flow in large arteries blood flow in the peripheral circulation and orthopedics obstetrics and respiration. The presentations are directed primarily to the clinical aspects of non invasive clinical measurements particularly the use of various aspects of ultrasound recordings. The applications of Doppler shift for measuring the adequacy of blood flow is emphasised. Impedance recording is discussed as are other graphic and semigraphic techniques for measuring blood flow primarily in the limbs. Unfortunately these editors fail to include in the discussion the importance of the history and physical examination or the conditions of the examining room and table and the patient's bed. The book is concerned primarily with blood flow in large blood vessels. The small peripheral vessels are not adequately considered. The use of plethysmography thermography and thermocouple or thermistor recordings are essentially ignored. This is to be expected because of the nature of the interest and applications intended. The discussions presented are good and should supplement very well other sources of study in the medical literature related to peripheral vascular disease.

**Exercise Testing of Cardiac Patients** By M Kaltenbach Baltimore Md 1976 The Williams & Wilkins Company 126 pp

This monograph of the series of *Monographs on Standardization of Cardio Angiological Methods* reviews in detail the various methods used for exercise testing of cardiac patients. The methods reviewed are numerous and clearly discussed. The treadmill used so extensively in the USA at present is not presented in detail. Nevertheless this 126 page paperback monograph is useful and should be carefully studied by all cardiologists. It outlines very well the many problems involved in exercise testing. Illustrations clearly show the direct relationship of oxygen consumption to the degree of exercise. The close positive relationship is to be expected but the findings do show the effectiveness of the exercise testing methods in recording the quantity of O<sub>2</sub> consumption according to the extent of exercise. It is evident from this book that the interpretation of the ECG obtained with exercise testing is often very difficult if not impossible. The fact that

the ECG changes reflect cardiac function with physical stress is interesting. These changes are simple to record and at times useful clinically. Because of the intense interest in exercise testing this book should be studied by all physicians who treat heart disease. This is a good book but unfortunately for physicians in the U.S.A. it contains only a brief discussion on the use of the treadmill exercise testing method.

**Cardiac Pacing** Edited by Yoshio Watanabe Amsterdam Oxford 1974 Excerpta Medica 601 pages

This book contains the papers presented at the Fifth International Symposium on Cardiac Pacing in Tokyo during March 1976. The papers are numerous and brief. They are concerned with cardiac electrophysiology. A V block hemodynamics of pacing as a diagnostic tool treatment of arrhythmias long term follow up of implanted pacemakers malfunction engineering and testing energy sources and electrodes. There are good sections of discussions and there is a good round table discussion on the question 'Is pacing prolonging life?' This question is discussed by contributors from several nations.

The book is a good one. Its importance is evidenced by the common use of pacing in medicine. It is unfortunate that each presentation is so brief. Nevertheless the reader will learn from this book the opinions on pacing from physicians throughout the world. It is a good book which is organized in the same manner as all other proceedings of meetings and symposia.

**The Evan Bedford Library of Cardiology Catalogue of Books Pamphlets and Journals** London 1977 Royal College of Surgeons

This is a catalogue of the excellent collection of the Library of Cardiology of Dr Evan Bedford of London. Those who knew Bedford admired him for his interest in fine things as well as for his ability as a bedside clinician. Bedford had been collecting rare books and other classics in cardiology for many years. This book lists the books and briefly describes the authors their interests and the contents of the various books. Many of these publications this reviewer had not known. The listing classification and description of the many (over 1000) books and pamphlets were extremely well done and with excellent taste Bedford wisely gave the collection to the Royal College of Physicians of London where they will remain where Bedford practiced and taught. This is a useful publication describing the contents of this fine collection.



- 2 Burch G E People live no longer anymore AM HEART J 53 285 1972
- 3 Goldstein S Sudden death and coronary heart disease Pathology of sudden death Mt Kisco N Y 1974 Futura Publishing Company
- 4 Burch G E and Giles T D Meticulous monitoring of all patients AM HEART J 51 438 1971

## MLAP LVEDP and left ventricular dysfunction

### To the Editor

We would like to make a comment on a statement mentioned by Kouchoukos and Karp in their excellent review of Management of the postoperative cardiovascular surgical patient (Am Heart J 92 513 531 1976). They stated that mean left atrial pressure (MLAP) in the absence of either stenosis or incompetence of the mitral valve approximates left ventricular end diastolic pressure (LVEDP) (page 517). This statement is true in the case of normal left ventricular (LV) function but it may not be so in patients with left ventricular dysfunction or in postoperative cardiovascular surgical patients since the LVEDP is not equal to MLAP in the presence of left ventricular disease. Braunwald and Frahm have shown that the difference between LVEDP and MLAP is between 1 and 18 mm Hg with an average of 9.0 mm Hg in all 21 patients with left ventricular disease in whom the pressures were measured none of these patients having mitral valve disease.

It is not uncommon to detect very high LVEDP in the range of 25 mm Hg or more in patients with coronary artery disease (CAD) while angina free yet they are not in congestive heart failure (CHF) indicating that their MLAP is lower than their LVEDP.

Ali Haddad M D  
Veterans Administration Hospital  
Iron Mountain Mich 49801  
Vassil K Prokhor M D  
Brooklyn Hospital  
Brooklyn N Y 11201

### REFERENCES

- 1 Braunwald E Brockenbrough E C et al Left atrial and left ventricular pressures in subjects without cardiovascular disease Circulation 24 267 1961
- 2 Braunwald E and Frahm C J Observations on the hemodynamic functions of the left atrium in man Circulation 24 633 1961

## Reply

### To the Editor

Drs Haddad and Prokhor are correct in pointing out that differences between left ventricular end diastolic pressure and mean left atrial pressure may exist in patients with left ventricular disease who are in normal sinus rhythm as described by Braunwald and Frahm.<sup>1</sup> However in a study of postoperative hemodynamics in 11 patients who had mitral valve replacement and in one patient who underwent excision of a left atrial myxoma by Rastelli and Kirklin<sup>2</sup> no statistically significant difference between 42 simultaneous determinations of mean left atrial pressure and left ventricular end diastolic pressure was observed. In this group of patients evidence for impaired cardiac function was present (i.e. low cardiac output and elevated left ventricular filling pressure). All but one of these patients were in atrial fibrillation. Our assumption is based on these observations and on observations of the response of measured left atrial pressure and cardiac output to infusion of volume vasodilating and inotropic drugs in a large number of postoperative cardiac surgical patients many of whom are described in our paper. While we agree that the measurement of mean left atrial pressure may not accurately reflect left ventricular end diastolic pressure in all circumstances it has proved a most useful parameter for assessment of cardiac performance postoperatively and as an index of the response to various interventions to increase preload decrease afterload and increase myocardial contractility.

Nicholas T Kouchoukos M D  
Robert B Karp M D  
University of Alabama in Birmingham  
Dept of Surgery  
Division of Cardiovascular and  
Thoracic Surgery  
University Station  
Birmingham Ala 35294

### REFERENCES

- 1 Braunwald E and Frahm C J Studies on Starling's law of the heart IV Observations on the hemodynamic functions of the left atrium in man Circulation 24 633 1961
- 2 Rastelli G C and Kirklin J W Hemodynamic state early after prosthetic replacement of mitral valve Circulation 34 448 1966

# American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*

Thomas D Giles *Assistant Editor*

## International Editorial Board

Walter H Abelman *Boston Mass*  
R P Ahlquist *Augusta*  
James K Alexander *Houston Texas*  
John H Barlow *Johannesburg South Africa*  
Giorgio Baroldi *Milan Italy*  
Lotfi L Ba'ta *Tulsa Okla*  
Thomas M Blake *Jackson Miss*  
S Gilbert Blount Jr *Denver*  
Bernardo Boskus *Argentina*  
Eugene I Charov *Moscow USSR*  
Henn Chevalier *Paris*  
Te Chuan Chou *Cincinnati*  
J M Criley *Torrance Calif*  
James A Cronvich *New Orleans*  
Anthony N Damato *Staten Island N Y*  
Arthur C DeGraff *New York*  
Lewis Dexter *Boston*  
James E Doherty *Little Rock*  
Charles Dubost *Paris*  
Jesse E Edwards *St Paul*  
Robert H Eich *Syracuse N Y*  
Mary Allen Enle *New York*  
Harvey Feigenbaum *Indianapolis*  
M Irene Ferrer *New York*  
Nancy C Flowers *Louisville*  
Nicholas J Fortun *Baltimore Md*  
Martin J Frank *Augusta Ga*  
Julian Frieden *New Rochelle N Y*  
Peter C Gazes *Charleston*  
Jacques Genest *Montreal Canada*  
Allan N Goodyer *New Haven Conn*  
Mervyn E Gotsman *Jerusalem Israel*  
Robert L Grissom *Omaha*  
Dale Groom *Oklahoma City*  
Rolf M Gunnar *Chicago*  
Warren G Guntheroth *Seattle Wash*  
E William Hancock *Stanford Calif*  
Herbert N Hultgren *Palo Alto Calif*

Mohamed Ibrahim *Cairo Egypt*  
Thomas N James *Birmingham Ala*  
L E January *Iowa City*  
James N Karnegs *Minneapolis*  
John A Kaster *Philadelphia*  
Nodar N Kipshidze *Tbilisi USSR*  
Richard Langendorf *Chicago*  
John H Laragh *New York*  
J Lequime *Brussels Belgium*  
Maunce Lev *Chicago*  
R J Linden *Leeds*  
F Loogen *Dusseldorf Germany*  
Hugh A McAllister Jr *Washington DC*  
Dan G McNamara *Houston*  
Rashid A Massum *Davis Calif*  
Clifford V Nelson *Portland Me*  
Eckhardt G J Olsen *London*  
Victor Parsonnet *Newark*  
Morton Lee Pearce *Los Angeles*  
Alfred Pick *Chicago*  
Hubert V Pipberger *Washington DC*  
Ray Pryor *Denver Colo*  
W Reynolds *Madison Wisc*  
Robert C Schlant *Atlanta Ga*  
Peter J Schwartz *Milano*  
Ralph C Scott *Cincinnati*  
J P Shillingford *London*  
Walter Somerville *London*  
Borys Surawicz *Lexington*  
Tadasu Takatsu *Osaka*  
John Thomas *Nashville Tenn*  
William H Wehrmacher *Chicago*  
Hen J J Wellens *Maastricht*  
*The Netherlands*  
Douglas P Zipes *Indianapolis Ind*

VOLUME 90

JANUARY-JUNE 1978

**An Atlas of Heart-Lead Coefficients** By Stanley Rush  
Hanover New Hampshire 1977 University Press of New  
England 211 pages Price \$45.00

**Vascular Surgery** 1st edition Edited by Robert B Ruther-  
ford MD Philadelphia 1977 W B Saunders Company  
1 401 pages Price \$65.00

**Doppler Ultrasonic Assessment of Cerebrovascular Disease**  
By Robert W Barnes and Michael R Wilson Iowa City 1975  
University of Iowa 187 pages

**Doppler Ultrasonic Assessment of Peripheral Arterial  
Disease** By Robert W Barnes and Michael R Wilson Iowa  
City 1976 University of Iowa 275 pages

## Announcements

---

### Continuing Education Symposium on Nutrition

The Division of Continuing Education in the Health  
Sciences Schools of Dentistry Medicine Nursing and Phar-  
macy University of California San Francisco and The  
Institute for the Study of Human Knowledge will present a  
symposium entitled *Nutrition Myths and Realities* to be  
held in San Francisco California on June 3 and 4 1978 The  
symposium is approved for AMA Category I credit For  
further information contact University of California San  
Francisco Continuing Education in Health Sciences 1308  
Third Ave San Francisco Calif 94143 Telephone (415) 666  
2894

### IX International Congress for Heart Research

The IX Congress of the International Society for Heart  
Research will be held in New Delhi India from September 28  
to October 2 1978 In addition to several Symposia and free  
communications there will be a competition for the Richard  
Bing Award for Young Investigators For inquiries please  
write to Prof P K Das Department of Physiology Faculty  
of Medicine University of Manitoba Winnipeg Canada R3E  
OW3

### Diagnostic Heart Imaging symposium

A symposium on Diagnostic Imaging of the Heart will be  
held at the Orlando Hyatt House Disneyworld Fla on  
August 2 through 6 1978 The symposium sponsored by the  
University of South Florida College of Medicine carries 20  
hours of AMA Category I credit Fee for physicians is \$170  
US funds fee for residents and technicians is \$95 US funds  
For further information contact Lawrence R Muroff MD  
Educational Symposia P O Box 17241 Tampa Fla 33682

### International symposium on exercise and cardiovascular function

The Czechoslovak Society for Rehabilitation and the  
Czechoslovak Society of Cardiology are organizing under the  
protection of the Rehabilitation Council of the International  
Cardiological Society President Prof Dr H Denolin an  
International Symposium on exercise and cardiovascular  
function to be held on October 11 through 13 1978 in  
Bratislava CSSR (Czechoslovakia) Topics will include

- (1) Influence of Exercise on Circulation (Physiological and  
Pathophysiological Aspects)
- (2) Exercise in the Rehabilitation Programs in Cardiovas-  
cular Diseases and
- (3) Free Communications

For further information contact Miroslav Palát MD  
Dept of Physical Medicine and Rehabilitation Derer's Hos-  
pital Lumbova ul 809 46 Bratislava Kramáre CSSR or  
Slovak Medical Society Congress Office Mickiewiczova 683  
22 Bratislava CSSR

### Information for authors

Most of the provisions of the Copyright Act of 1976 became  
effective on January 1 1978 Therefore all manuscripts must  
be accompanied by the following statement signed by each  
author *The undersigned author(s) transfers all copyright  
ownership of the manuscript entitled (title of article) to The  
C V Mosby Company in the event the work is published The  
author(s) warrants that the article is original is not under  
consideration by another journal and has not been previously  
published Authors will be consulted when possible  
regarding republication of their material*

# Author index\*

A

- ABDEL FATTAH M M ABOU ZENIA A NOMEIR A M  
BADAWI H AND SALAH M Intrapulmonary  
acetylcholine in bilharzial cor pulmonale 141
- ABERNATHY WILLIAM S FERRIER GREGORY R AND MOE  
GORDON K The influence of atrial systole on  
ventricular capture by failing artificial pacemakers  
II Experimental observations 499
- AND LEPECHKIN E The influence of atrial activity on  
ventricular capture by failing artificial pacemakers  
I Report of two new cases and review of the  
literature 502
- ABOU ZENIA A (See Abdel Fattah et al) 141
- ABRAHAM C FURMAN K I AND SALANT D Analgesic  
abuse and microvascular changes 768 (Annot)
- ADOMIAN GERALD E LAKS MICHAEL M AND BILLINGHAM  
M E The incidence and significance of contrac-  
tion bands in endomyocardial biopsies from  
normal human hearts 348
- ADSON MARTIN A (See Radtke et al) 235
- AHMED S SULTAN (See Ettinger et al) 555
- GUPTA R C AND BRANCATO RUSSELL R Significance of  
nausea and vomiting during acute myocardial  
infarction 671 (Annot)
- ANTALIAN AGOP HANBY ROBERT I HOFFMAN IRWIN  
WEISS DANIEL VOLETI CHOUDARY AND WISOFF  
B GEORGE Significance of new Q waves after  
bypass grafting Correlations between graft paten-  
cy ventriculogram and surgical venting tech-  
nique 479
- AKHTAR MASOOD DAMATO ANTHONY N RUSKIN JEREMY  
N BATSFORD WILLIAM P REDDY C PRATAP  
TICZON ANDRES R DHATT MALKIAT S LOMES  
JOSEPH A C AND CALON ANTONIO H Ante-  
grade and retrograde conduction characteristics in  
three patterns of paroxysmal atrioventricular  
junctional reentrant tachycardia 92
- AKHTAR RIAZ A (See Spodick et al) 247
- ALONSO DANIEL H (See Andrade et al) 316
- ALPERT J S (See Warren Alpert and Francis) 130  
(Annot)
- AMAT Y LEON FERNANDO AND ROSEN KENNETH M Reply  
413 (Letter to Editor)
- ANDERSON GARY J (See Levites Baker and Anderson)  
747
- ANDRADE SONIA G (See Andrade et al) 316
- ANDRADE ZILTON A ANDRADE SONIA G OLIVEIRA  
GEORGE B AND ALONSO DANIEL R Histopathol-  
ogy of the conducting tissue of the heart in Chagas  
myocarditis 316
- ANGELAKOS EVANGELOS T (See Nelson et al) 220
- ANGERPOINTER T A (See Lewis et al) 301
- ANSLY JOSEPH D (See Heymsfield et al) 584
- ARONOW WILBERT H (See Danshy and Aronow) 474
- STEINBERG EDWARD A WOOD BYRON ZWEIF STEPHEN  
TSAO KE PING AND RAGGIO LOUIS Carbon  
monoxide and ventricular fibrillation threshold in  
dogs with acute myocardial injury 154

B

- BABBS CHARLES F Effect of pentobarbital anesthesia on  
ventricular defibrillation threshold in dogs 331
- BADAWI H (See Abdel Fattah et al) 141
- BAKER THOMAS (See Levites Baker and Anderson) 747
- BARLOW H T C Appropriate therapy of hypertension in the  
elderly 809 (Annot)
- BARLOW JOHN B (See Cohen et al) 697
- BEEVERS D G (See Ferriss et al) 375
- (See Ferriss et al) 641

- BERNARD ROLAND (See WHO/ISC Task Force et al) 796
- BERSON ALAN S HAISTY W KENNETH AND PIPBERGER  
HUBERT V Electrode position effects on Frank  
lead electrocardiograms 463
- BETHEL ROBERT A (See Heymsfield et al) 584
- BETRIU AMADEO (See Navarro Lopez et al) 369
- BIRLE LESLIE (See Carlson et al) 3-2
- BILLINGHAM M E (See Adomian Laks and Billingham)  
348
- BLOOM MARTIN C (See Castellanos et al) 228
- BOEKHOUT MUSSERT M J BRIET E VAN BRUNNEN P.  
LEMKES H H P J AND LOELIGER E A Arterial  
thromboembolic complications with aortic ball  
valve prostheses 20 (Letter to Editor)
- BONNER R ALAN (See Nelson et al) 220
- BOSCHUNG PRISKA (See Burckhardt et al) 187
- BRANCATO RUSSELL R (See Ahmed Gupta and Brancato)  
611 (Annot)
- BRASHEAR RICHARD F AND YU PAO LO Components of the  
hemodynamic response to elevated cerebrospinal  
fluid pressure 111
- BRIET E (See Boekhout Mussert et al) 270 (Letter to  
Editor)
- BROWY J J (See Ferriss et al) 375
- (See Ferriss et al) 641
- BROWSE NORMAN L Natural fibrinolysis 417
- BRYNJOLFSSON GISSLE (See Nemickas et al) 76
- BUDA A J LEVENE D L MYERS M G CHISHOLM A W  
AND SHANE S J Coronary artery spasm and  
mitral valve prolapse 45
- BULKLEY BERNADINE H AND HUTCHINS GROVER M Acute  
postoperative graft phlebitis A rare cause of  
saphenous vein-coronary artery bypass failure  
757
- KLACSMANN PETER G AND HUTCHINS GROVER M  
Angina pectoris myocardial infarction and sudden  
cardiac death with normal coronary arteries A  
clinopathologic study of 9 patients with progres-  
sive systemic sclerosis 563
- BURCH G H Of diastolic and systolic pressure and left  
ventricular work 406 (Annot)
- Of plastic materials in clinical medicine 197 (Annot)
- Of teaching hygiene 535 (Annot)
- Of the mind of man 769 (Annot)
- Of the sham operation 674 (Annot)
- Of why the two heart pumps are anatomically united to  
form one heart 811 (Annot)
- The role of the central nervous system in chronic con-  
gestive heart failure 255
- BURCH K H (See Saravolatz et al) 163
- BURCKHARDT DIETER STAUB JEAN-JACQUES KRAENZLIN  
MARTIN RAIDER ERNST ENGEL URS AND CLOP  
FENBERG PETER, with the technical assistance of  
Boschung Priska The systolic time intervals in  
thyroid dysfunction 187
- BURWELL LAWRENCE H (See Newton and Burwell) 126  
(Annot)

C

- CALON ANTONIO H (See Akhtar et al) 29
- CARLSON C JEFFREY EMILSON BIANKA AND RAPAPORT  
ELLIOT with the technical assistance of Bible  
Leslie Creatine phosphokinase MB isoenzyme in  
hypothermia Case reports and experimental stud-  
ies 359
- CASTELLANOS AGUSTIN SUNG RUEY J MALLON STEPHEN  
M BLOOM MARTIN G AND MYERBURG ROBERT J  
Effects of proximal intra atrial Wenckebach on  
distal atrioventricular nodal and His-Purkinje  
block With special reference to the theory of  
alternating Wenckebach periods 228
- CATINCHI F MARTINEZ (See Johnson and Catincchi) 359
- CHAN LINDA S (See Harrison et al) 483

VOLUME 95  
COPYRIGHT © 1978 BY  
THE C V MOSBY COMPANY  
*All rights reserved*

Printed in the United States of America

# Author index\*

A

- ABDEL FATTAH M M ABDOU ZENIA A NOMEIR A M  
BADAWI H AND SALAH M Intrapulmonary  
acetylcholine in bilharzial cor pulmonale 141
- ABERNATHY WILLIAM S FERRIER GREGORY II AND MOE  
GORDON K The influence of atrial systole on  
ventricular capture by failing artificial pacemak-  
ers. II Experimental observations, 489
- AND LEPSCHIK E The influence of atrial activity on  
ventricular capture by failing artificial pacemak-  
ers I Report of two new cases and review of the  
literature 509
- ABOL ZENIA A (See Abdel Fattah et al) 141
- ABRAHAM C FIRMAN K I AND SALANT D Analgesic  
abuse and microvascular changes 268 (Annot)
- ADOMIAN GERALD E LAKS MICHAEL M AND BILLINGHAM  
M E The incidence and significance of contrac-  
tion bands in endomyocardial biopsies from  
normal human hearts 343
- ADON MARTIN A (See Radtke et al) 235
- AKHED S ULTAN (See Ettinger et al) 55
- GUPTA R C AND BRANCATO RUSSELL R Significance of  
nausea and vomiting during acute myocardial  
infarction 671 (Annot)
- ALYABLANI AGOP HANBY ROBERT I HOFFMAN IRWIN  
WEISS DANIEL VOLETI CHOUDARY AND WISOFF  
B GEORGE Significance of new Q waves after  
bypass grafting Correlations between graft paten-  
cy ventriculogram and surgical venting tech-  
nique 499
- AKHTAR MASOOD DAMATO ANTHONY N RUSKIN JEREMY  
N BATSFORD WILLIAM P REDDY C PRATAP  
TICZON ANDRES R DHATT MALKIAT S GOWES  
JOSEPH A C AND CALON ANTONIO H Ante  
grade and retrograde conduction characteristics in  
three patterns of paroxysmal atrioventricular  
junctional reentrant tachycardia 29
- AKHTAR RIAZ A (See Spodick et al) 247
- ALONSO DANIEL R (See Andrade et al) 316
- ALPERT J S (See Warren Alpert and Francis) 130  
(Anno)
- AMAT Y LEON FERNANDO AND ROSEN KENNETH M Reply  
413 (Letter to Editor)
- ANDERSON GARY J (See Leites Baker and Anderson)  
747
- ANDRADE SONIA G (See Andrade et al) 316
- ANDRADE ZITTON A ANDRADE SONIA G OLIVEIRA  
GEORGE B AND ALONSO DANIEL R Histopathol-  
ogy of the conducting tissue of the heart in Chagas  
myocarditis 316
- ANGELAKOS EVANGELOS T (See Nelson et al) 220
- ANGERPOINTER T A (See Lewis et al) 301
- ANSLEY JOSEPH II (See Heymsfield et al) 584
- ARONOW WILBERT S (See Danahy and Aronow) 474
- STEINER EDWARD A WOOD BYRON ZWIG STEPHEN  
TEAO KE FENG AND RAGGIO LOUIS Carbon  
monoxide and ventricular fibrillation threshold in  
dogs with acute myocardial injury 54

B

- BABBS CHARLES F Eff ect of pentobarbital anesthesia on  
ventricular defibrillation threshold in dogs 331
- BADAWI H (See Abdel Fattah et al) 141
- BAKER THOMAS (See Levites Baker and Anderson) 747
- BARLOW D T C Appropriate therapy of hypertension in the  
elderly 809 (Annot)
- BARLOW JOHN B (See Cohen et al) 687
- BEEVERS D G (S e Ferriss et al) 3 5
- (S e Ferriss et al) 641

- BERNARD ROLAND (See WHO/ISC Task Force et al) 796
- BERSON ALAN S HAISTY W KENNETH AND PIPBERGER  
HUBERT V Electrode position effects on Frank  
lead electrocardiograms 463
- BETHEL ROBERT A (See Heymsfield et al) 584
- BETHU AMADEO (See Navarro Lopez et al) 369
- BIBLE LESLIE (See Nelson et al) 352
- BILLINGHAM M E (See Adomian Laks and Billingham)  
348
- BLOOM MARTIN G (See Castellanos et al) 2 9
- BOEKHOUT MUSSERT M J BRIET H VAN BRUMMELEN P  
LEMMES H H P J, AND LOELLIGER E A Arterial  
thromboembolic complications with aortic ball  
valve prostheses 270 (Letter to Editor)
- BONNER R ALAN (See Nelson et al) 220
- BOSCHUNG PRISKA (See Burckhardt et al) 187
- BRANCATO RUSSELL R (See Ahmed Gupta and Brancato)  
671 (Annot)
- BRASHEAR, RICHARD E AND YU PAO-LO Components of the  
hemodynamic response to elevated cerebral fluid  
pressure 52
- BRIET F (See Boekhout Mussert et al) 270 (Letter to  
Editor)
- BROWN J J (See Ferriss et al) 310
- (See Ferriss et al) 641
- BROWSE NORMAN L Natural fibrinolysis 417
- BRYNOLFSSON GISELA (See Nemickas et al) 766
- BUDA A J LEVENE D L MYERS M G CHISHOLM A W  
AND SHANE S J Coronary artery spasm and  
mitral valve prolapse 457
- BULLEY BERNARDINE H AND HUTCHINS GROVER M Acute  
postoperative graft phlebitis A rare cause of  
saphenous vein-coronary artery bypass failure  
787
- KLACHMAN PETER G AND HUTCHINS GROVER M  
Angina pectoris myocardial infarction and sudden  
cardiac death with normal coronary arteries A  
clinicopathologic study of 9 patients with progres-  
sive systemic sclerosis 563
- BURCH F Of diastolic and systolic pressure and left  
ventricular work 406 (Annot)
- Of plastic materials in clinical medicine 127 (Annot)
- Of teaching hygiene 535 (Annot)
- Of the mind of man 269 (Annot)
- Of the sham operation 674 (Annot)
- Of why the two heart pumps are anatomically united to  
form one heart 811 (Annot)
- The role of the central nervous system in chronic con-  
gestive heart failure 253
- BURCH K H (See Saravolatz et al) 163
- BURCKHARDT DIETER STAUB JEAN JACQUES KRAENZLIN  
MARTIN RAEDER ERNST ENGEL URS AND CLOP-  
FENBURG PETER, with the technical assistance of  
Boschung Priska The systolic time intervals in  
thyroid dysfunction 187
- BURWELL, LAWRENCE R (See Newton and Burwell) 126  
(Annot)

C

- CALON ANTONIO H (See Akhtar et al) 2
- CARLSON C JEFFREY EMILSON BIANKA AND RAPAPORT  
ELLIOT with the technical assistance of Bible  
Leslie Crestine phosphokinase MB isoenzyme in  
hypothermia Case reports and experimental stud-  
ies 357
- CASTELLANOS AGUSTIN SONG RUEY J MAILLOV STEPHEN  
M BLOOM MARTIN G AND MYERBURG ROBERT J  
Effects of proximal intra atrial Wenckebach on  
distal atrioventricular nodal and His-Purkinje  
block With special reference to the theory of  
alternans, Wenckebach periods 278
- CATINCHI F MARTINEZ (See Johnson and Catinchi) 359
- CHAN LINDA S (See Harrison et al) 483

- CHANDRARATNA P A N AND LANGEVIN EUGENE On the significance of an abnormal P terminal force in Lead V, 267 (Annot.)
- AND SAN PEDRO S B Echocardiographic features of the normal and malfunctioning porcine xenograft valve 548
- CHAO T C (See Teoh et al) 683
- CHAWLA KAMAL K CRUZ JAIRO KRAMER NEIL E AND TOWNE WILLIAM D Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia Report of a patient with normal coronary arteriograms 637
- CHESLER ELLIOT MITHA ABDUL S WEIR E KENNETH MATISON RODNEY E AND HITCHCOCK PETER J Myocardial infarction in the Black population of South Africa Coronary arteriographic findings 691
- CHIA B L (See Teoh et al) 683
- CHIPPERFIELD BARBARA AND CHIPPERFIELD J R Differences in metal content of the heart muscle in death from ischemic heart disease 732
- CHIPPERFIELD J R (See Chipperfield and Chipperfield) 732
- CHISHOLM A W (See Buda et al) 457
- CHRISTODOULOU JAMES (See Frishman et al) 169
- CINCA JUAN (See Navarro Lopez et al) 369
- CLOPPENBURG PETER (See Burckhardt et al) 187
- COHEN JULES (See Scherf and Cohen) 536 (Annot.)
- COHEN LAWRENCE S (See Langou et al) 295
- COHEN MICHAEL V The functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance collateral flow 396
- COHEN MORRIS POCOCK WENDY A LAMIER JEFFREY H McLAREN MARGARET J LACHMAN ANTHONY S AND BARLOW JOHN B Four year follow up of Black schoolchildren with non ejection systolic clicks and mitral systolic murmurs 697
- COHN PETER F (See Lindsey and Cohn) 441
- COLEMAN R EDWARD (See Klein Roberts and Coleman) 659
- COLTART D J (See Lewis et al) 301
- COTOI GEORGESCU C AND COZLEA P Retrograde Wenckebach phenomenon in ventricular tachycardia 676 (Letter to Editor)
- COUMEL PHILIPPE (See WHO/ISC Task Force et al) 796
- COUSINS A LUCIAN EDDLEMAN E E JR AND REEVES T JOSEPH Prediction of aortic valvular area and gradient by noninvasive techniques 308
- COX F (See Saravolatz et al) 163
- COZLEA P (See Cotoi Georgescu and Cozlea) 676 (Letter to Editor)
- CRUZ JAIRO (See Chawla et al) 637
- CURTIS EDWARD I HEIBEL RICHARD H AND SHAVER JAMES A Autonomic maneuvers in hereditary Q T interval prolongation (Romano Ward syndrome) 420
- D
- DALE JON Reply 272 (Letter to Editor)
- DALTON WILLARD (See Nemickas et al) 766
- DAMANI PABODH M (See Puto et al) 807 (Annot.)
- DAMATO ANTHONY N (See Akhtar et al) 22
- (See WHO/ISC Task Force et al) 796
- DANAHY DANIEL T AND ARONOW WILBERT S Lidocaine induced cardiac rate changes in atrial fibrillation and atrial flutter 474
- DAVIDSON ALLAN MCMURTRY IVAN AND REEVES J T Pulmonary vascular effects of verapamil 810 (Annot.)
- DAVIES D L (See Ferriss et al) 375
- DE LA CRUZ CATALINO JR (See Ettinger et al) 555
- DELUZ PROTASIO L (See Diamond et al) 204
- DE MEDINA ETIENNE O ROBLES (See WHO/ISC Task Force et al) 796
- DESILVA REGIS A VERRIER RICHARD L AND LOWN BERNARD The effects of psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog 197
- DEVOS MICHAEL D SR (See Jones et al) 738
- DHATT MALKIAT S (See Akhtar et al) 22
- DIAMOND GEORGE A FORRESTER JAMES H DELUZ PROTASIO L WYATT H L AND SHAW H J C Post extrasystolic potentiation of ischemic myocardium by atrial stimulation 204
- DICTER RICHARD (See van der Bakh et al) 627
- DONALDSON II J At home or to hospital? 406 (Annot.)
- DOYLE JOSEPH T (See Nemati et al) 12
- DREIFUS LEONARD S (See Spodick et al) 247
- DUBACH U C (See Knaus et al) 602
- DUNN ROSALIE A (See Nemati et al) 12
- DUPONT ELISE (See Jones et al) 738
- II
- ECANOW BERNARD AND GOLD BERNARD H The problem of cell aggregation during coronary artery bypass procedures 535 (Annot.)
- EDDLEMAN E E JR (See Cousins Eddleman and Reeves) 308
- EDMISTON W ALLAN (See Harrison et al) 483
- EMILSON BIANKA (See Carlson et al) 352
- ENGEL URS (See Burckhardt et al) 187
- ENGELMAN RICHARD M Myocardial edema a complication of ischemic arrest during cardiopulmonary bypass 128 (Annot.)
- ENSSLEN ROLAND (See Schwarz et al) 146
- (See Schwarz et al) 570
- (See Thomann et al) 725
- EPSTEIN STEPHEN E (See Spray et al) 811
- ETTINGER PHILIP O WU CHIA F DE LA CRUZ CATALINO JR WEISSE ALLEN H AHMED S SULTAN AND REGAN TIMOTHY J Arrhythmias and the Holiday Heart Alcohol associated cardiac rhythm disorders 555
- F
- FARIS JAMES V MCHENRY PAUL L AND MORRIS STEPHEN N Concepts and applications of treadmill exercise testing and the exercise electrocardiogram 102
- FARNSWORTH A E (See Lewis et al) 301
- FAZZINI PIERFILIPPO More on effectiveness of the CCU 813 (Letter to Editor)
- FELLOWS KENNETH E JR (See Rocchini et al) 497
- FELNER J M (See Heymsfield et al) 283
- (See Heymsfield et al) 584
- FENG P II (See Teoh et al) 683
- FERRIER GREGORY R (See Abernathy Ferrer and Moe) 489
- FERRISS J N BEEVERS D G BROWN J J DAVIES D L FRASER R LEVER A F Clinical biochemical and pathological features of low renin (primary) hyperaldosteronism 375
- — — FRASER R LEVER A F PADFIELD P L AND FERRISS J N Low renin (primary) hyperaldosteronism Differential diagnosis and distinction of sub groups within the syndrome 641
- FISCH CHARLES (See WHO/ISC Task Force et al) 796
- FISHER H (See Saravolatz et al) 163
- FISHMAN DAVID (See Nemickas et al) 766
- FLAMING WILLEM (See Schwarz et al) 146
- (See Schwarz et al) 570
- FOLTS JOHN D (See Gallagher et al) 338
- FORRESTER JAMES S (See Diamond et al) 204
- FRANCIS H S (See Warren Alpert and Francis) 130 (Annot.)
- FRASER R (See Ferriss et al) 375
- (See Ferriss et al) 641
- FREIS EDWARD D (See Shah, Khatn and Freis) 611
- FRIEND PETER S A unique antibody response associated with the development of membranous nephropathy in systemic lupus erythematosus 672 (Annot.)
- FRISHMAN WILLIAM H CHRISTODOULOU JAMES WEKSLER BARBETTE SMITH CHARLES KILLIP THOMAS AND SCHEIDT STEPHEN Abrupt propranolol with drawal in angina pectoris Effects on platelet aggregation and exercise tolerance 169

- FULTON RICHARD ■ (See Radtke et al.) 235  
 FURMAN K I (See Abrahams Furman and Salant) 268 (Annot.)  
 FURMAN SEYMOUR, AND WHITMAN RICHARD Cardiac pacing and pacemakers IX. Statistical analysis of pace maker data 115  
 FURUKAWA SOICHI (See Hashimoto et al.) 619

G

- GALLAGHER KIM P., FOLTS JOHN D ROWE GEORGE G *With the technical assistance of Shebuski Ronald* Comparison of coronary arteriograms with direct measurements of stenosed coronary arteries in dogs 338  
 GARDNER A M N Inferior vena caval interruption in the prevention of fatal pulmonary embolism 69  
 GASCHO JOSEPH A AND NEWTON MAURY C JR. Electro magnetic interference in dynamic electrocardiography caused by an electric blanket 408 (Annot.)  
 GEORGESCU C (See Cotoi, Georgescu and Cozlea) 676 (Letter to Editor)  
 GIBBS DANIEL M (See Heymsfield et al.) 584  
 GILKESON GARY STONE MARVIN J WATERMAN MICHAEL TING RUBY GOMEZ SANCHEZ CELSO E HULL ALAN AND WILLERSON JAMES T Detection of myoglobin by radioimmunoassay in human sera its usefulness and limitations as an emergency room screening test for acute myocardial infarction 70  
 GLENV WILLIAM W L (See Langou et al.) 295  
 GOLD BERNARD H (See Ecanow and Gold) 535 (Annot.)  
 GOMES JOSEPH A C (See Akhtar et al.) 2?  
 GOMEZ SANCHEZ CELSO E (See Gilkeson et al.) 70  
 GOODWIN J F International cardiology 279  
 GOODYEAR MICHAEL Menstruation and heart disease 675 (Letter to Editor)  
 GRAMIAK RAYMOND (See Reeves Nanda and Gramiak) 578  
 GREENBLATT DAVID J Reply 542 (Letter to Editor)  
 GUNNAR, ROLF M (See Nemickas et al.) 766  
 GUPTA, R C (See Ahmed Gupta and Brancato) 671 (Annot.)

H

- HADDAD ALI Potassium and salt substitutes 134 (Letter to Editor)  
 — AND PROKHOR VASSIL K MLAP LVEDP and left ventricular dysfunction 814 (Letter to Editor)  
 HAISTY V KENNETH (See Berson Haisty and Pipberger) 463  
 HALPERN M J Fructose and triglycerides 540 (Letter to Editor)  
 HAMAMOTO HIROMU (See Hashimoto et al.) 619  
 HAMBY ROBERT I (See Antablian et al.) 429  
 HAN JAOK AND YOON MYUNG S Reply 13? (Letter to Editor)  
 HARRISON EARL C ROSCHKE E JOHN MEYER HARVEY I EMMISTON W ALLAN CHAN LINDA S TATNER DOROTHY AND LAU FRANCIS Y K Cholelithiasis A frequent complication of artificial heart valve replacement 433  
 HASHIMOTO KENICHI HAMAMOTO HIROMU HONDA YUICHI RO HIROSE MASARU FURUKAWA SOICHI AND KIMURA EIICHI Changes in components of kinn system and hemodynamics in acute myocardial infarction 619  
 HEIBEL RICHARD H (See Curtis Heibel and Shaver) 40  
 HEYMSFIELD S B MCNISH T PERKINS J V AND FELNER J M Sequence of cardiac changes in Duchenne muscular dystrophy 233  
 — BETHEL ROBERT A ANSLEY JOSEPH D GIBBS DANIEL M FELNER JOEL M AND NUTTER DONALD O Cardiac abnormalities in cachectic patients before and during nutritional repletion 584  
 HIRATA YUKIO (See Iwamura et al.) 60  
 HIROSAWA KOSHICHIRO (See Horie Sekiguchi and Hiroawa) 81

- HIROSE MASARU (See Hashimoto et al.) 619  
 HITCHCOCK PETER J (See Chesler et al.) 691  
 HJALMARSON AKE C (See Waldenstrom Hjalmarson and Thornell) 43  
 HODES RICHARD M Sudden deaths from IHD by age and sex 413 (Letter to Editor)  
 HODGKIN BRIAN C (See Nelson et al.) 220  
 HOFFMAN IRWIN (See Antablian et al.) 4?9  
 HONDA YUICHIRO (See Hashimoto et al.) 619  
 HONOUR A J (See Littler et al.) 180  
 HORIE TOSHIMORU SEKIGUCHI MORIE AND HIROSAWA KOSHICHIRO Relationship between myocardial infarction and preinfarction angina A histopathological study of coronary arteries in two sudden death cases employing serial section 81  
 HOSSACK K F AND NEILSON GRAEME Influence of etiology on the functional result of aortic valve replacement 454  
 HULL ALAN (See Gilkeson et al.) 70  
 HUME L AND REUBEN ■ R The effects of exercise on the amplitude of the first heart sound in normal subjects 4  
 HUTCHINS GROVER M (See Bulkley Kiacsmann and Hutchins) 563  
 — (See Bulkley and Hutchins) 757

I

- IMHOFF P R (See Kraus et al.) 602  
 IONESCU MARIAN I (See Tandon Smith and Ionescu) 595  
 ISTANBULLU ASIM AND VELDET SUHA Excitation contraction abnormalities and heart block 275 (Letter to Editor)  
 IWAMURA NOBUTAKI KODAMA ITSUO SHIMIZU TAKESHI HIRATA YUKIO TOYAMA JUNJI AND YAMADA KAZUO Functional properties of the left septal Purkinje network in premature activation of the ventricular conduction system 60

J

- JOHNSON CHARLES ■ AND CATINCHI F MARTINEZ The prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis 369  
 JOHINEN C (See Ruonio et al.) 70?  
 JONES CARL E DEVIOUS MICHAEL D SR THOMAS JOHN X JR AND DUPONT ELISE The effect of chronic cardiac denervation on infarct size following acute coronary occlusion 738

K

- KALEFLEISCH JOHN H STOWE DAVID F AND SMITH JAMES J Evaluation of the heart rate response to the Valsalva maneuver 707  
 KARP ROBERT B (See Kouchoukos and Karp) 814 (Letter to Editor)  
 KENNEDY RICHARD J References—dog's tails? 2/4 (Letter to Editor)  
 KHATRI IBRAHIM (See Shah Khatri and Freis) 611  
 KILLIP THOMAS (See Frishman et al.) 169  
 — (See Nemickas et al.) 766  
 KIMURA EIICHI (See Hashimoto et al.) 619  
 KINOSHITA SHINJI Mechanism of concealed trigeminy 410 (Letter to Editor)  
 — Parasympathetic and re entry 812 (Letter to Editor)  
 KLACSMANN PETER G (See Bulkley Kiacsmann and Hutchins) 563  
 KLEIN MILTON S ROBERTS ROBERT AND COLEMAN R EDWARD Radionuclides in the assessment of myocardial infarction 659  
 KLINE IRWIN K (See Spodick et al.) 247  
 KLOTZ HOWARD H Aortic valve prostheses rheumatic fever and lone atrial regurgitation 275 (Letter to Editor)  
 KNALS M PRISTER B DUBACH U C AND IMHOFF P R Human pharmacology studies with a new orally active stimulant of cardiac adrenergic beta receptors 607



- KOCH WESER, JAN The comeback of hydralazine 1  
 KODAMA ITSUO (See Iwamura et al) 60  
 KOLMAN BENET S VERRIER RICHARD L AND LOWN  
 BERNARD Effect of vagus nerve stimulation on  
 ventricular fibrillation threshold 132 (Letter to  
 Editor)  
 KONNO SOUJI (See Takayasu Obunai and Konno) 154  
 KOUCHOUKOS NICHOLAS T AND KARP ROBERT II Reply  
 814 (Letter to Editor)  
 KRAENZLIN MARTIN (See Burckhardt et al) 187  
 KRAKOFF LAWRENCE R (See Viachakis Ribeiro and  
 Krakoff) 78  
 KRAMER NEIL E (See Chawla et al) 637  
 KRIKLER DENNIS (See WHO/ISC Task Force et al) 796  
 KUHN LESLIE A Management of shock following acute  
 myocardial infarction Part I Drug therapy 529  
 — Management of shock following acute myocardial infarction  
 Part II Mechanical circulatory assistance  
 789

L

- LACHMAN ANTHONY S (See Cohen et al) 697  
 LAForge RALPH L More on high school health curricula 272  
 (Letter to Editor)  
 LAKIER JEFFREY II (See Cohen et al) 697  
 LAKS MICHAEL M (See Adomian Laks and Billingham)  
 348  
 LANGEVIN EUGENE (See Chandraratna and Langevin) 267  
 (Annot)  
 LANGOU RENE A COHEN LAWRENCE S SHEPS DAVID  
 WOLFSON STEVEN AND GLENN WILLIAM W L  
 Ondines Curse Hemodynamic response to dia  
 phragm pacing (electrophrenic respiration) 295  
 — (See Sostman and Langou) 775  
 LAU FRANCIS Y K (See Harrison et al) 483  
 LEE ST GEORGE T JR Nitroglycerin ointment therapy and  
 leg edema 273 (Letter to Editor)  
 LEMKES II H F J (See Boekhout Mussert et al) 270  
 (Letter to Editor)  
 LEPECHSKIN E (See Abernathy and Lepeschkin) 502  
 LEVENE D L (See Buda et al) 457  
 LEVER A F (See Ferriss et al) 375  
 — (See Ferriss et al) 641  
 LEVITE RAFAEL, BAKER THOMAS AND ANDERSON GARY J  
 The significance of hypotension developing during  
 treadmill exercise testing 747  
 LEVY MATTHEW N Reply 411 (Letter to Editor)  
 LEWIS G R J WILSON P A POOLE ANGERPONTER T A  
 FARNSWORTH A E WILLIAMS II T AND  
 COLTART D J Measurement of the circulatory  
 effects of dobutamine a new inotropic agent in  
 patients following cardiac surgery 301  
 LIEDTKE A JAMES (See Pinto et al) 807 (Annot)  
 LIGHTFOOT PAUL R Reply 813 (Letter to Editor)  
 LINDSEY H EUGENE JR AND COHN PETER F Silent  
 myocardial ischemia during and after exercise test  
 ing in patients with coronary artery disease 441  
 LITTLER W A WEST M J HONOUR A J AND SLEIGHT P  
 The variability of arterial pressure 180  
 LITTMANN L (See Tenczer and Littmann) 270 (Letter to  
 Editor)  
 LIVINGSTON PHILIP H Preceptorships at major medical  
 centers 413 (Letter to Editor)  
 LOCKWOOD W R (See McNeill Strong and Lockwood)  
 448  
 LOELIGER, E A (See Boekhout Mussert et al) 270 (Letter to  
 Editor)  
 LONDON G M SAFAR M E WEISS Y A AND SIMON CH  
 A Total effective compliance of the vascular bed in  
 essential hypertension 325  
 LONG HERBERT D (See van der Bel Kahn et al) 627  
 LOWENSTEIN JEROME AND STEELE JOHN M JR Prazosin  
 262  
 LOWN BERNARD (See Kolman Verner and Lown) 132  
 (Letter to Editor)  
 — (See DeSilva Verner and Lown) 197

M

- McCAUGHAN DONALD (See Nemati et al) 12  
 McHENRY PAUL L (See Farris McHenry and Morris) 107  
 McLAREN MARGARET J (See Cohen et al) 697  
 MACMILLAN ROBERT M AND STRATE RANDALL W Fibrin  
 deposition on a pacemaker catheter in a heparin  
 ized patient 405 (Annot)  
 McMURTRY IVAN (See Davidson McMurry and Reeves)  
 810 (Annot)  
 McNEILL K MILLS STRONG JAMES E JR AND LOCKWOOD  
 W R Bacterial endocarditis An analysis of  
 factors affecting long term survival 448  
 McNISH T (See Heymsfield et al) 283  
 MADHAVAN T (See Saravolatz et al) 163  
 MADIAS JOHN E Use of precordial ST segment mapping 96  
 MAGRIÑA JORGE (See Navarro Lopez et al) 369  
 MALLON STEPHEN M (See Castellanos et al) 228  
 MARIN E (See Moro et al) 243  
 MARON BARRY J (See Spray et al) 511  
 MASON P (See Ferriss et al) 375  
 MATISONN RODNEY E (See Chesler et al) 691  
 MAZUR NICOLAI A (See WHO/ISC Task Force et al) 796  
 MEIJLER FRITS L (See WHO/ISC Task Force et al) 796  
 MELBIN JULES (See Noordergraaf and Melbin) 545  
 MENDLOWITZ MILTON The hypertension complex 389  
 MENEFEE MAX G (See van der Bel Kahn et al) 627  
 MEYERS HARVEY I (See Harrison et al) 483  
 MILVY PAUL Statistics marathoning and CHD 538  
 (Annot)  
 MITCHELL, J R A (See Morris and Mitchell) 139  
 MITHA ABDUL S (See Chesler et al) 691  
 MOE GORDON K (See Abernathy Ferrer and Moe) 489  
 MOGENSEN LARS (See WHO/ISC Task Force et al) 796  
 MOGHADAM A N (See Spodick et al) 247  
 MORET PIERRE (See WHO/ISC Task Force et al) 796  
 MORO C MARIN E SANCHEZ A AND SOLOZABAL J  
 Pulmonary varix Report of a case with additional  
 anomalies of the vascular pulmonary tree 243  
 MORRIS G KEITH AND MITCHELL, J R A Can death from  
 venous thromboembolism be prevented in elderly  
 patients with hip fractures 139  
 MORRIS STEPHEN N (See Farris McHenry and Morris)  
 102  
 MORROW ANDREW G (See Spray et al) 511  
 MYERBURG ROBERT J (See Castellanos et al) 228  
 MYERS M G (See Buda et al) 457

N

- NADAS ALEXANDER S (See Rocchini et al) 497  
 NANDA NAVIN C (See Reeves Nanda and Gramiak) 578  
 NAVARRO LOPEZ FRANCISCO CINCA JUAN SANZ GINFA  
 PERIZ ALBERTO MAGRIÑA JORGE AND BETRIU  
 AMADEO Isolated T wave alternans 389  
 NEILSON GRAEVE (See Hossack and Neilson) 454  
 NEILSON CLIFFORD V HODGKIN BRIAN C BOWNER R  
 ALAN AND ANGELAS EVANGELOS T The differ  
 ence vector Assessment of effects of changes or  
 interventions 220  
 NEMATI MASSOUD DOYLE JOSEPH T McCAUGHAN  
 DONALD DUNN ROSALIE A AND PIPBERGER  
 HUBERT V The orthogonal electrocardiogram in  
 normal women Implications of sex differences in  
 diagnostic electrocardiography 12  
 NEVICKAS RINGAUDAS FISHMAN DAVID KILLIP THOMAS  
 DALTON WILLARD BRYNJOLFSSON GISSUR ROB  
 INSON JOHN AND GUNNAR ROLF M Massive  
 myocardial necrosis in a young woman 766  
 (GPC)  
 NEURATH OTTO Overdiagnosis of left anterior hemiblock 675  
 (Letter to Editor)  
 NEVILLE A M (See Ferriss et al) 375  
 NEWTON MAURY C JR AND BURWELL LAWRENCE II  
 Single coronary artery with myocardial infarction  
 and mitral regurgitation 176 (Annot)  
 — (See Gascho and Newton) 408 (Annot)  
 NOVEIR A M (See Abdel Fattah et al) 141

NOORDERGRAAF ABRAHAM AND MELBIN JULES Ventricular afterload, a succinct yet comprehensive definition 545

NUTTER, DONALD O (See Heymans Id et al) 584

# O

OBUNAI YOSHIO (See Takayasu Obunai, and Konno) 154

OLIVEIRA GEORGE B (See Andrade et al) 316

O'Rourke MICHAEL Differences in Coronary Care Units 2,0 (Letter to Editor)

# P

PADFIELD P L (See Ferrus et al) 641

PAYOT MAURICE (See Silverman Payot and Stanger) 761

PENTILA U (See Raunio et al) 109

PERIZ ALBERTO (See Navarro Lopez et al) 369

PERRINS J V (See Heymansfeld et al) 983

PISTER, H (See Knaus et al) 609

PIVTO EDWARD L DAMANI PRABODH M STERNBERG CORA N AND LIETKE A JAMES Fine flutterings of the aortic valve as demonstrated by aortic valve echocardiograms, 807 (Annot)

PITTSBERGER, HUBERT V (See Nemati et al) 12

— (See Benson Hasty and Pittsberger) 463

PISA ZATNEK (See WHO/ISC Task Force et al) 796

POCOCK WENDY A (See Cohen et al) 697

PORDY LEON Computerized electrocardiography 135 (Letter to Editor)

PRESS ARTHUR J (See Spodick et al) 247

PROKHOR VASSIL K (See Haddad and Prokhov) 814 (Letter to Editor)

PLECH F Indirect recording of left atrial activation in the main pulmonary trunk 412 (Letter to Editor)

# Q

QUINN F L (See Saravolatz et al) 163

# R

RADTKE WALLACE E SMITH HUGH C FULTON RICHARD F AND ADSON MARTIN A Misdiagnosis of aortic septal defect in patients with hereditary telangiectasia (Oiler Weber Rendu disease) and hepatic arteriovenous fistulas 235

RAEDER, ERNST (See Reichhardt et al) 187

RACIO LOUIS (See Aronow et al) 754

RAPAPORT ELLIOT (See Carlson et al) 352

RAUNIO H RISSANEN V JOKINEN C AND PENTILA O Significance of a terminal R wave in Lead V of the electrocardiogram 702

REDDY C PRATAP (See Akhtar et al) 22

REEVES J T (See Davidson McMurtry and Reeves) 810 (Annot)

REEVES T JOSEPH (See Cousins Eddleman and Reeves) 308

REEVES WILLIAM C NANDA NAVIN C AND GRAMIAK RAYMOND Echocardiography in chronic alcoholics following prolonged periods of abstinence 518

REGAN TIMOTHY J (See Ettinger et al) 555

REIBSEN S H (See Hume and Reibsen) 4

RIBEIRO ARTUR H (See Vlachakos Ribeiro and Krakoff) 75

RISSANEN V (See Raunio et al) 709

ROBERTS ROBERT AND SOBEL BURTON E Creatine kinase isoenzymes in the assessment of heart disease 591

— (See Klein Roberts, and Coleman) 69

ROBERTS WILLIAM C (See Spray et al) 311

ROBERTSON J I S (See Ferrus et al) 35

— (See Ferrus et al) 641

ROBINSON JOHN (See Nemickas et al) 766

ROCCHINI ALBERT P, ROSENTHAL AMNON SCHUSTER SAMUEL, FELLOWS KENNETH E JR AND NADAS ALEXANDER S Systemic hypertension after surgical treatment of a congenital arteriovenous malformation 497

ROSCHKE F JOHN (See Harrison et al) 483

ROSEN KENNETH M (See Amat y Leon and Rosen) 413 (Letter to Editor)

ROSENTHAL AMNON (See Rocchini et al) 497

ROSSI LINO "Salvage the pacemaker" at autopsy 540 (Letter to Editor)

— (See Thiene Valente and Rossi) 716

ROWE GEORGE G (See Gallagher et al) 338

RLSKIN JEREMY N (See Akhtar et al) 22

# S

SAFAR, M E (See London et al) 375

SALAH M (See Abdel Fattah et al) 141

SALANT D (See Abrahams Furman and Salant) 268 (Annot)

SANCHEZ A (See Moro et al) 243

SAN PEDRO S B (See Chandrasekhar and San Pedro) 548

SANZ GINES (See Navarro Lopez et al) 369

SARAVOLATZ L D BURCH K H QUINN J I COX F MADHAVAN T AND FISHER E Polymicrobial infective endocarditis. An increasing clinical entity 163

SAY BURHAN AND WILSEY CARLA E Chromosome aberration in ectopia cordis (46 XX 1,q+) 274 (Letter to Editor)

SCHIEDT STEPHEN (See Frishman et al) 169

SCHERF DAVID AND COHEN JULES To each according to his desert 536 (Annot)

SCHERPE A (See Strauer and Scherpe) 210

SCHLEPFER MARTIN (See Schwarz et al) 146

SCHOENFELD MYRON R Needed An FDA for surgery? 540 (Letter to Editor)

SCHUSTER SAMUEL (See Rocchini et al) 497

SCHWARTZ FRANZ FLAMENG WILHELM THORMANN JOCHEN ENSLEEN ROLAND SESTO MICHAEL AND SCHLEPFER MARTIN Cardiac reserve during isoproterenol stress in patients with aortic valve disease before and after corrective surgery 146

— — ENSLEEN ROLAND SESTO MICHAEL AND THORMANN JOCHEN Effect of coronary collaterals on left ventricular function at rest and during stress 570

— (See Thormann et al) 725

SEELY STEPHEN Venture research 133 (Letter to Editor)

— Blood donors and coronary disease 671 (Letter to Editor)

SEKIGUCHI MORIE (See Horie Sekiguchi and Hirose) 81

SESTO MICHAEL (See Schwarz et al) 146

— (See Schwarz et al) 510

— (See Thormann et al) 725

SHAH SHAUKAT KHATRI IBRAHIM AND FREIS EDWARD D Mechanism of antihypertensive effect of thiazide diuretics 611

SHANE S J (See Buda et al) 457

SHAYER JAMES A (See Curtius Heibel and Shayer) 420

SHERBUSHKI RONALD (See Gallagher et al) 338

SHERP DAVID (See Langou et al) 295

SHIMIZU TAKESHI (See Iwanaga et al) 60

SILVERMAN NORVAN H PAYOT MAURICE AND STANGER PAUL Stimulated tricuspid valve echoes in tricuspid atresia 161

SIMON CH A (See London et al) 325

SLEIGHT P (See Littler et al) 180

SMITH DONALD R (See Tandon Smith and Ionescu) 595

SMITH HUGH C (See Radtke et al) 235

SMITH JAMES J (See Kalbfleisch Stowe and Smith) 707

SMITH CHARLES (See Frishman et al) 169

SOBEL BURTON E (See Roberts and Sobel) 521

SOLOZAR, J (See Moro et al) 243

- SOSTMAN H DIRK AND LANGOU RENE A Contemporary medical management of stable angina pectoris 775
- SPENCER FRANK C A plea for early open mitral commissurotomy 668
- SPODICK DAVID H KLINE IRWIN K PRESS ARTHUR J MOGHADAM A N AHTAR RIAZ A AND DREIFUS LEONARD E Clinical pathologic conference 247
- SPRAY THOMAS L MARON BARRY J MORROW ANDREW G EPSTEIN STEPHEN E AND ROBERTS WILLIAM C A discussion on hypertrophic cardiomyopathy 511
- STANGER PAUL (See Silverman Payot and Stanger) 761
- STAUB JEAN JACQUES (See Burckhardt et al) 187
- STEELE JOHN M JR (See Lovenstein and Steele) 262
- STEINBERG S M (See Warren and Steinberg) 541 (Letter to Editor)
- STEMMER EDWARD A (See Aronow et al) 754
- STEPHAN EDOUARD Hereditary bundle branch system defect. Survey of a family with four affected generations 89
- STERNBERG CORA N (See Pinto et al) 807 (Annot)
- STONE MARVIN J (See Gilkeson et al) 70
- STOWE DAVID F (See Kalbfleisch Stowe and Smith) 707
- STRATE RANDALL W (See MacMillan and Strate) 405 (Annot)
- STRAUER H E AND SCHERPE A Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease 210
- STRONG JAMES E JR (See McNeill Strong and Lockwood) 448
- SUNG RUEY J (See Castellanos et al) 228
- SWAN H J C (See Diamond et al) 204

T

- TAKAYASU SHUNSUKE OBUNAI YOSHIO AND KONNO SOUJI Clinical classification of Ebstein's anomaly 154
- TAMBYAH J A (See Teoh et al) 683
- TAN L K A (See Teoh et al) 683
- TANDON ANAND P SMITH DONALD R AND IONESCU MARIAN I Hemodynamic evaluation of the Ionescu Shiley pericardial xenograft in the mitral position 595
- TATTER DOROTHY (See Harrison et al) 483
- TENCZER J AND LITTMANN L Differential refractoriness of ventricular specialized conduction system 270 (Letter to Editor)
- TEOH P C TAN L K A CHIA H L CHAO T C TAMBYAH J A AND FENG P H Non specific aorto arteritis in Singapore with special reference to hypertension 683
- THIENE GAETANO VALENTE MARIALUISA AND ROSSI LINO Involvement of the cardiac conduction system in pericarditis nodosa 716
- THOMAS JOHN X JR (See Jones et al) 738
- THORMANN JOCHEN (See Schwarz et al) 146
- (See Schwarz et al) 570
- SCHWARZ FRANZ ENSSLEN ROLAND AND SESTO MICHAEL Vagal tone significance of electrophysiologic findings and clinical course in symptomatic sinus node dysfunction 725
- THORNELL LARS (See Waldenström Hjalmarsson and Thornell) 43
- TICZON ANDRES H (See Akhtar et al) 22
- TING RUBY (See Gilkeson et al) 70
- TOWNE WILLIAM D (See Chawala et al) 637
- TOYAMA JUNJI (See Iwamura et al) 60
- TSAO KE PING (See Aronow et al) 754

V

- VALENTE MARIALUISA (See Thiene Valente and Rossi) 716
- VAN BRUMMELEN P (See Boekhout Mussert et al) 270 (Letter to Editor)

- VAN DER BEL KAHN JOHANNA M WATANAKURAKORN CHATTRAI MENEFEE MAX G LONG HERBERT D AND DICHTER RICHARD Chlamydia trachomatis endocarditis 627
- VELDET SUHA (See Istanbuli and Veldet) 2/5 (Letter to Editor)
- VERRIER RICHARD L (See Kolman Vernier and Lown) 137 (Letter to Editor)
- (See DeSilva Vernier and Lown) 197
- VLACHAKIS NICHOLAS D RIBEIRO ARTUR B AND KRAKOFF LAWRENCE R Effect of saralasin upon plasma catecholamines in hypertensive patients 78
- VOLETI CHOUDARY (See Aintablian et al) 429

W

- WALDENSTRÖM ANDERS P HJALMARSSON A&E C AND THORNELL LARS A possible role of noradrenaline in the development of myocardial infarction. An experimental study in the isolated rat heart 43
- WARD CHRISTOPHER Rheumatic heart disease psittacosis and the importance of epidemiology 266 (Annot)
- WARREN S E ALPERT J S AND FRANCIS G S Diet in the Coronary Care Unit 130 (Annot)
- AND STEINBERG S M Reactions to furosemide 541 (Letter to Editor)
- WATANAKURAKORN CHATTRAI (See van der Bel Kahn et al) 627
- WATERNAN MICHAEL (See Gilkeson et al) 70
- WEIR E KENNETH (See Chesler et al) 691
- WEISS MORRIS M Wolff Parkinson White (Type B) Ebstein's anomaly and congenital ichthyosis 133 (Letter to Editor)
- WEISS Y A (See London et al) 325
- WEISSE ALLEN B (See Ettlinger et al) 555
- WEISZ DANIEL (See Aintablian et al) 429
- WEKSLER BABETTE (See Frishman et al) 169
- WELLES HEIN J J (See WHO/ISC Task Force et al) 796
- WEST M J (See Littler et al) 180
- WHITMAN RICHARD (See Furman and Whitman) 115
- (WHO/ISC Task Force) DE MEDINA ETIENNE O ROBLES BERNARD ROLAND COUMEL PHILIPPE DAMATO ANTHONY N FISCH CHARLES KRIEGER DENNIS MAZUR NICOLAI A MEINLER FRITS L MOGENSEN LARS MORET PIERRE PISA ZBYNEK AND WELLES HEIN J J Definition of terms related to cardiac rhythm 796
- WILLERSON JAMES T (See Gilkeson et al) 70
- WILLIAMS H T (See Lewis et al) 301
- WILSEY CARLA E (See Say and Wilsey) 274 (Letter to Editor)
- WILSON P A POOLE (See Lewis et al) 301
- WISOFF H GEORGE (See Aintablian et al) 429
- WOLFSON STEVEN (See Langou et al) 295
- WOOD BYRON (See Aronow et al) 754
- WU CHIA F (See Ettlinger et al) 555
- WYATT H L (See Diamond et al) 204

Y

- YAMADA KAZUO (See Iwamura et al) 60
- YOKOYAMA MASAYOSHI Increase of WBC CRP and BSR following cardiac pacemaker implant 671 (Annot)
- YOON MYUNG S (See Jaok and Yoon) 132 (Letter to Editor)
- YU PAO LO (See Brashear and Yu) 52

Z

- ZWEIG STEPHEN (See Aronow et al) 754

# Subject index\*

A

- Aberration chromosome in ectopia cordis (46 XX,1,q+) (Say and Wilsey) 274 (Letter to Editor)
- Abnormal P terminal force in Lead V on the significance of an (Chandraratna and Langevin) 267 (Annot)
- Abstinence echocardiography in chronic alcoholics following prolonged periods of (Reeves Nanda and Gramiak) 578
- Abuse analgesic and microvascular changes (Abrahams Furman and Salant) 568 (Annot)
- According to his desert to each (Scherf and Cohen) 536 (Annot)
- Acetylcholine intrapulmonary in bilateral cor pulmonale (Abdel Fattah et al) 141
- Activation left atrial indirect recording of in the main pulmonary trunk (Puech) 412 (Letter to Editor)
- Reply (Amat y Leon and Rosen) 413
- Acute myocardial infarction caused by hyperkalemia electrocardiographic changes simulating report of a patient with normal coronary arteriograms (Chawla et al) 637
- changes in components of kunitz system and hemodynamics in (Hashimoto et al) 619
- management of shock following Part I Drug therapy (Kuhn) 529
- significance of nausea and vomiting during (Ahmed Gupta and Brancato) 671 (Annot)
- Adrenergic beta receptors cardiac human pharmacology studies with a new orally active stimulant of (Kass et al) 609
- Afterload, ventricular a succinate yet comprehensive definition (Noordergraaf and Melbin) 545
- Age and sex sudden deaths from IHD by (Hodes) 413 (Letter to Editor)
- Aggregation cell during coronary artery bypass procedures the problem of (Ecanow and Gold) 535 (Annot)
- Alcohol associated cardiac rhythm disorders arrhythmias and the Holiday Heart (Ettinger et al) 555
- Alcoholics chronic echocardiography in following prolonged periods of abstinence (Reeves Nanda and Gramiak) 578
- Alternans isolated T wave (Navarro Lopez et al) 369
- Amplitude of the first heart sound effects of exercise on the normal subjects (Hume and Reuben) 4
- Analgesic abuse and microvascular changes (Abrahams Furman and Salant) 568 (Annot)
- Anatomically united to form one heart of why the two heart pumps are (Burch) 811 (Annot)
- Anesthesia pentobarbital on ventricular defibrillation threshold in dogs effect of (Babbs) 331
- Angina pectoris abrupt propranolol withdrawal in effects on platelet aggregation and exercise tolerance (Fishman et al) 189
- myocardial infarction and sudden cardiac death with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klemm and Hutchins) 563
- stable contemporary medical management of (Sostman and Langou) 775
- preinfarction relationship between myocardial infarction and a histopathological study of coronary arteries in two sudden death cases employing serial section (Horie Sekiguchi and Hiroawa) 81
- Announcements 138 278 416 544 678 816
- Anomaly Ebstein's clinical classification of (Takayama Obana, and Honno) 154
- Antegrade and retrograde conduction characteristics in 3 patterns of paroxysmal atrioventricular junctional reentrant tachycardia (Akhtar et al) 29
- Anterior hemiblock left overdiagnosis of (Neurath) 675 (Letter to Editor)
- Antibody response a unique associated with the development of membranous nephropathy in systemic lupus erythematosus (Fried) 679 (Annot)
- Antihypertensive effect of thiazide diuretics mechanism of (Shah Khatri, and Freis) 611
- Aortic ball valve prostheses arterial thromboembolic complications with (Boekhout Mussert et al) 270 (Letter to Editor)
- Reply (Dale) 271
- regurgitation lone aortic valve prostheses rheumatic fever and (Kloth) 275 (Letter to Editor)
- valve disease cardiac reserve during isoproterenol stress in patients with before and after corrective surgery (Schwarz et al) 146
- echocardiograms fine flutterings of the aortic valve as demonstrated by (Pinto et al) 807 (Annot)
- fine flutterings of as demonstrated by aortic valve echocardiograms (Pinto et al) 807 (Annot)
- prostheses rheumatic fever and lone aortic regurgitation (Kloth) 275 (Letter to Editor)
- replacement influence of etiology on the functional result of (Hosack and Nelson) 454
- valvular area and gradient prediction of by noninvasive techniques (Cousins Eddleman and Reeves) 308
- Aorto arteritis non specific in Singapore with special reference to hypertension (Teoh et al) 683
- Appropriate therapy of hypertension in the elderly (Barlow) 809 (Annot)
- Arrest ischemic myocardial edema a complication of during cardiopulmonary bypass (Engelman) 178 (Annot)
- Arrhythmias and the Holiday Heart Alcohol associated cardiac rhythm disorders (Ettinger et al) 555
- Arterial pressure the variability of (Littler et al) 180
- thromboembolic complications with aortic ball valve prostheses (Boekhout Mussert et al) 270 (Letter to Editor)
- Reply (Dale) 1
- Arteriograms, coronary comparison of with direct measure ments of stenosed coronary arteries in dogs (Gallagher Folts and Rowe) 338
- normal report of a patient with electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia (Chawla et al) 637
- Arteriographic findings coronary of myocardial infarction in the Black population of South Africa (Chesler et al) 691
- Arteriovenous fistulas hepatic and hereditary telangiectasia (Osler Weber Rendu disease) misdiagnosis of atrial septal defect in patients with (Radkic et al) 235
- malformation congenital systemic hypertension after surgical treatment of a (Rocchini et al) 497
- Artery(ies) bypass failure coronary saphenous vein acute postoperative graft phlebitis a rare cause of (Bulkley and Hutchins) 77
- procedures coronary the problem of cell aggregation during (Ecanow and Gold) 535 (Annot)
- coronary normal angina pectoris myocardial infarction and sudden cardiac death with a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klemm and Hutchins) 563
- disease coronary silent myocardial ischemia during and after exercise testing in patients with (Lindsey and Cohn) 411
- ventricular function and coronary hemodynamics after intravenous nitroglycerin in (Strauer and Scherpe) 210
- spasm coronary and mitral valve prolapse (Buda et al) 457

Artery(ies)—continued

- stenosed coronary in dogs comparison of coronary arteriograms with direct measurements of (Gallagher, Folts and Rowe) 338
- Artificial heart valve replacement cholelithiasis a frequent complication of (Harrison et al) 483
- pacemakers failing influence of atrial activity on ventricular capture by I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 502
- of atrial systole on ventricular capture by II Experimental observations (Abernathy, Ferner and Moe) 489
- At home or to hospital? (Donaldson) 406 (Annot)
- Atresia tricuspid simulated tricuspid valve echoes in (Silverman, Payot and Stanger) 761
- Atrial activation left indirect recording in the main pulmonary trunk (Puech) 412 (Letter to Editor)
- Reply (Amat y Leon and Rosen) 413
- activity on ventricular capture by failing artificial pacemakers influence of I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 502
- fibrillation and atrial flutter lidocaine induced cardiac rate changes in (Danahy and Aronow) 474
- flutter and atrial fibrillation lidocaine induced cardiac rate changes in (Danahy and Aronow) 474
- septal defect misdiagnosis of in patients with hereditary telangiectasia (Osler, Weber, Rendu disease) and hepatic arteriovenous fistula (Radtke et al) 235
- stimulation post extrasystolic potentiation of ischemic myocardium by (Diamond et al) 204
- systole on ventricular capture by failing artificial pacemakers influence of II Experimental observations (Abernathy, Ferner and Moe) 489
- Atroventricular junctional reentrant tachycardia paroxysmal antegrade and retrograde conduction characteristics in 3 patterns of (Akhtar et al) 22
- nodal distal and His Purkinje block effects of proximal intra atrial Wenckebach on With special reference to the theory of alternating Wenckebach periods (Castellanos et al) 228
- Autonomic maneuvers in hereditary Q T interval prolongation (Romano Ward syndrome) (Curtiss, Heibel and Shaver) 420
- Autopsy salvage the pacemaker at (Rosy) 540 (Letter to Editor)

B

- Bacterial endocarditis an analysis of factors affecting long term survival (McNeill, Strong and Lockwood) 448
- Ball valve prostheses aortic arterial thromboembolic complications with (Boekhout, Mussert et al) 270 (Letter to Editor)
- Reply (Dale) 271
- Bands contraction in endomyocardial biopsies from normal human hearts incidence and significance of (Adomian, Laks and Billingham) 348
- Beta receptors cardiac adrenergic human pharmacology studies with a new orally active stimulant of (Knaus et al) 602
- Bilateral cor pulmonale intrapulmonary acetylcholine in (Abdel Fattah et al) 141
- Biochemical clinical and pathological features of low renin (primary) hyperaldosteronism (Ferriss et al) 375
- Biopsies endomyocardial from normal human hearts incidence and significance of contraction bands in (Adomian, Laks and Billingham) 348
- Black population of South Africa myocardial infarction in the coronary arteriographic findings (Chester et al) 691
- schoolchildren with non-ejection systolic clicks and mitral systolic murmurs four year follow up of (Cohen et al) 697

- Blanket electric electromagnetic interference in dynamic electrocardiography caused by an (Gascho and Newton) 408 (Annot)
- Block heart excitation-contraction abnormalities and (Istanbullu and Veldet) 275 (Letter to Editor)
- His Purkinje and distal atrioventricular nodal effects of proximal intra atrial Wenckebach on With special reference to the theory of alternating Wenckebach periods (Castellanos et al) 228
- Blood donors and coronary disease (Seely) 675 (Letter to Editor) (Reply to Goodyear p 675)
- Book reviews 136 277 414 543 677 815
- Books received 137 278 415 544 678 816
- Branch system defect bundle hereditary Survey of a family with four affected generations (Stephan) 89
- BSR WBC and CRP following cardiac pacemaker implant increase of (Yokoyama) 671 (Annot)
- Bundle branch system defect hereditary Survey of a family with four affected generations (Stephan) 89
- Bypass cardiopulmonary myocardial edema a complication of ischemic arrest during (Engelman) 128 (Annot)
- failure coronary artery saphenous vein acute postoperative graft phlebitis a rare cause of (Bulkeley and Hutchins) 757
- grafting significance of new Q waves after correlations between graft patency ventriculogram and surgical venting (Antablian et al) 429
- procedures coronary artery the problem of cell aggregation during (Ecanow and Gold) 535 (Annot)

C

- Cachectic patients cardiac abnormalities in before and during nutritional repletion (Heymsfield et al) 584
- Capture ventricular by failing artificial pacemakers influence of atrial activity on I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 502
- of atrial systole on II Experimental observations (Abernathy, Ferner and Moe) 489
- Carbon monoxide and ventricular fibrillation threshold in dogs with acute myocardial injury (Aronow et al) 764
- Cardiac abnormalities in cachectic patients before and during nutritional repletion (Heymsfield et al) 584
- adrenergic beta receptors human pharmacology studies with a new orally active stimulant of (Knaus et al) 602
- changes in Duchenne muscular dystrophy sequence of (Heymsfield et al) 283
- conduction system involvement of the in paraneoplastic nodal (Thiene, Valente and Rossi) 716
- death sudden angina pectoris and myocardial infarction with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkeley, Klagsmann and Hutchins) 563
- denervation effect of chronic on infarct size following acute coronary occlusion (Jones et al) 738
- pacemaker implant increase of WBC CRP and BSR following (Yokoyama) 671 (Annot)
- pacing and pacemakers IX Statistical analysis of pacemaker data (Furman and Whitman) 115
- rate changes in atrial fibrillation and atrial flutter lidocaine induced (Danahy and Aronow) 474
- reserve during isoproterenol stress in patients with aortic valve disease before and after corrective surgery (Schwarz et al) 146
- rhythm definition of terms related to (WHO/ISC Task Force—see also de Medina et al) 796 (Special report)
- disorders alcohol associated arrhythmias and the Holiday Heart (Ettlinger et al) 555
- surgery measurement of the circulatory effects of dobutamine a new inotropic agent in patients following (Lewis et al) 301

Cardiology international (Goodwin) 279

- Cardiomyopathy hypertrophic a discussion on (Clinical pathologic conference) (Spray et al) 511
- Cardiopulmonary bypass myocardial edema a complication of ischemic arrest during (Engelman) 128 (Annot)
- Care Unit Coronary diet in the (Warren Alpert and Francis) 140 (Annot)
- differences in (O'Rourke) 270 (Letter to Editor)
- Catecholamines plasma in hypertensive patients effect of saralasin upon (Vlachakis Ribeiro and Krakoff) 18
- Catheter pacemaker fibrin deposition on a heparinized patient (MacMillan and Strate) 40s (Annot)
- (CU) (coronary care unit) more on effectiveness of the (Fazzini, Marchi and Pucci) 813 (Letter to Editor)
- Cell aggregation during coronary artery bypass procedures the problem of (Ecanow and Gold) 535 (Annot)
- Central nervous system in chronic congestive heart failure the role of the (Burch) 255
- Cerebrospinal fluid pressure elevated components of the hemodynamic response to (Brashear and Yu) 53
- Chagas myocarditis histopathology of the conducting tissue of the heart in (Andrade et al) 316
- CHD statistics and marathon (Milvy) 538 (Annot)
- Chlamydia trachomatis* endocarditis (van der Bel Kahn et al) 677
- Cholelithiasis a frequent complication of artificial heart valve replacement (Harrison et al) 483
- Chromosome aberration in ectopia cordis (46,XX,1q+) (Say and Wisley) 214 (Letter to Editor)
- Chronic alcoholics echocardiography in following prolonged periods of abstinence (Reeves Nanda and Gramiak) 518
- congestive heart failure role of the central nervous system in (Burch) 255
- Circulatory assistance mechanical Management of shock following acute myocardial infarction Part II (Kuhn) 189
- effects of dobutamine a new inotropic agent in patients following cardiac surgery measurement of the (Lewin et al) 301
- Classification clinical of Ebstein's anomaly (Takayasu Obunai, and Konno) 154
- Clinical biochemical and pathological features of low renin (primary) hyperaldosteronism (Ferrus et al) 315
- classification of Ebstein's anomaly (Takayasu Obunai and Konno) 154
- entity-polymicrobial infective endocarditis an increasing (Saravolatz et al) 163
- medicine of plastic materials in (Burch) 127 (Annot)
- pathologic conference (Spodick et al) 247
- (Spray et al) 511 A discussion of hypertrophic cardiomyopathy
- (Nemickas et al) 766 Massive myocardial necrosis in a young woman
- Collateral(s) coronary effect of on left ventricular function at rest and during stress (Schwarz et al) 510
- functional value of in myocardial ischemia and therapeutic approach to enhance collateral flow (Cohen) 396
- flow functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance (Cohen) 396
- Comeback of hyaluronate the (Koch Weser) 1
- Commissurotomy mitral, early open a plea for (Spencer) 668
- Complex the hypertension (Mendelowitz) 389
- Compliance total effective of the vascular bed in essential hypertension (London et al) 375
- Complication(s) arterial thromboembolic with aortic ball valve prosthesis (Boekhout Mussert et al) 210 (Letter to Editor)
- Reply (Dale) 271
- of artificial heart valve replacement, cholelithiasis a frequent (Harrison et al) 483
- Computerized electrocardiography (Pordy) 135 (Letter to Editor)
- Concealed trigeminy mechanism of (Kinoshita) 410 (Letter to Editor)
- Reply (Levy) 411
- Conducting tissue of the heart in Chagas myocarditis histopathology of the (Andrade et al) 316
- Conduction aspects of hypokalemia prominent electrocardiographic in a patient with periodic paralysis (Johnson and Catinech) 359
- characteristics antegrade and retrograde in 3 patterns of paroxysmal atrioventricular junctional reentrant tachycardia (Akhtar et al) 22
- system, cardiac involvement of the in paratuberculosis nodosa (Thiene Valente and Rossi) 716
- ventricular functional properties of the left septal Purkinje network in premature activation of the (Iwamura et al) 60
- specialized differential refractoriness of (Tenczer and Littmann) 270 (Letter to Editor)
- Conference clinical pathologic (Spodick et al) 247
- (Spray et al) 511 A discussion on hypertrophic cardiomyopathy
- (Nemickas et al) 766 Massive myocardial necrosis in a young woman
- Congenital arteriovenous malformation systemic hypertension after surgical treatment of a (Rocchini et al) 497
- ichthyosis Wolff Parkinson White (Type B) and Ebstein's anomaly (Weiss) 133 (Letter to Editor)
- Congestive heart failure chronic role of the central nervous system in (Burch) 255
- Contemporary medical management of stable angina pectoris (Sostman and Langou) 775
- Contraction bands in endomyocardial biopsies from normal human hearts, incidence and significance of (Adomian Laks and Balingham) 348
- excitation abnormalities and heart block (Istanbullu and Veldek) 275 (Letter to Editor)
- Cor pulmonale bilateral intrapulmonary acetylcholine in (Abdel Fattah et al) 141
- Cordis ectopia (46,XX,17q+) chromosome aberration in (Say and Wisley) 274 (Letter to Editor)
- Coronary arteriograms comparison of with direct measurements of stenosed coronary arteries in dogs (Callagher Folts and Rowe) 338
- normal report of a patient with electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia (Chawla et al) 617
- arteriographic findings of myocardial infarction in the Black population of South Africa (Chester et al) 691
- artery(ies) bypass failure saphenous vein acute postoperative graft phlebitis a rare cause of (Bulkley and Hutchins) 557
- procedures the problem of cell aggregation during (Ecanow and Gold) 535 (Annot)
- disease silent myocardial ischemia during and after exercise testing in patients with (Landsey and Cohn) 441
- ventricular function and coronary hemodynamics after intravenous nitroglycerin in (Strauer and Scherpel) 210
- histopathological study of employing serial section Relationship between myocardial infarction and preinfarction angina (Horie Seikichi, and Hirokawa) 81
- normal, angina pectoris, myocardial infarction and sudden cardiac death with a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klagsmann and Hutchins) 563
- single with myocardial infarction and mitral regurgitation (Newton and Burwell) 126 (Annot)
- spasm and mitral valve prolapse (Buda et al) 457
- stenosed in dogs comparison of coronary arteriograms with direct measurements of (Callagher Folts and Rowe) 338

## Coronary—continued

- care unit(s) (CCU) more on effectiveness of the (Fazzini Marchi and Pucci) 813 (Letter to Editor)
- diet in the (Warren Alpert and Francis) 130 (Annot)
- differences in (O'Rourke) 270 (Letter to Editor)
- collaterals effect of on left ventricular function at rest and during stress (Schwarz et al) 570
- functional value of in myocardial ischemia and therapeutic approach to enhance collateral flow (Cohen) 396
- disease blood donors and (Seely) 675 (Letter to Editor) (Reply to Goodyear p 675)
- hemodynamics and ventricular function after intravenous nitroglycerin in coronary artery disease (Strauer and Scherpe) 210
- occlusion acute effect of chronic cardiac denervation on infarct size following (Jones et al) 738
- Creatine kinase isoenzymes in the assessment of heart disease (Roberts and Sobel) 521
- phosphokinase MB isoenzyme in hypothermia case reports and experimental studies (Carlson Emilson and Rapaport) 352
- CRP WBC and BSR following cardiac pacemaker implant increase of (Yokojama) 671 (Annot)
- Curricula high school health more on (LaForge) 272 (Letter to Editor)

## D

- Death(s) from venous thromboembolism be prevented in elderly patients with hip fractures can? (Morris and Mitchell) 139
- sudden cardiac angina pectoris and myocardial infarction with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkeley Klacsmann and Hutchins) 563
- from IHD by age and sex (Hodes) 413 (Letter to Editor)
- Defibrillation threshold ventricular in dogs effect of pentobarbital anesthesia on (Babbs) 331
- Definition of terms related to cardiac rhythm (WHO/ISC Task Force—see also de Medina et al) 796 (Special report)
- Denervation cardiac effect of chronic on infarct size following acute coronary occlusion (Jones et al) 738
- Deposition fibrin on a pacemaker catheter in a heparinized patient (MacMillan and Strate) 405 (Annot)
- Desert to each according to his (Scherf and Cohen) 536 (Annot)
- Diaphragm pacing (electrophrenic respiration) hemodynamic response to—Ondine's curse (Langou et al) 295
- Diastolic and systolic pressure and left ventricular work of (Burch) 406 (Annot)
- Diet in the Coronary Care Unit (Warren Alpert and Francis) 130 (Annot)
- Difference(s) in Coronary Care Units (O'Rourke) 270 (Letter to Editor)
- vector the assessment of effects of changes or interventions (Nelson et al) 220
- Differential refractoriness of ventricular specialized conduction system (Tenczer and Littmann) 270 (Letter to Editor)
- Direct measurements of stenosed coronary arteries in dogs comparison of coronary arteriograms with (Galagher Folta and Rowe) 338
- Discussion on hypertrophic cardiomyopathy a (Clinical pathologic conference) (Spray et al) 511
- Disease heart menstruation and (Goodyear) 675 (Letter to Editor)
- Reply (Blood donors and coronary disease) (Seely) 675
- Diuretics thiazide mechanism of antihypertensive effect of (Shah Khatri and Fres) 611
- Dobutamine a new inotropic agent in patients following cardiac surgery measurement of the circulatory effects of (Lewis et al) 301

- Dogs tails—references? (Kennedy) 274 (Letter to Editor)
- Donors blood and coronary disease (Seely) 675 (Letter to Editor) (Reply to Goodyear p 675)
- Drug therapy Management of shock following acute myocardial infarction I (Kuhn) 529
- Duchenne muscular dystrophy sequence of cardiac changes in (Heymsfield et al) 283
- Dynamic electrocardiography electromagnetic interference in caused by an electric blanket (Gascho and Newton) 408 (Annot)
- Dysfunction left ventricular MIAP LVEDP and (Haddad and Prokhov) 814 (Letter to Editor)
- Reply (Kouchoukos and Karp) 814
- thyroid the systolic time intervals in (Burckhardt et al) 187
- Dystrophy Duchenne muscular sequence of cardiac changes in (Heymsfield et al) 283

## E

- Early open mitral commissurotomy a plea for (Spencer) 668
- Ebstein's anomaly clinical classification of (Takajasu Obunai and Konno) 154
- Wolff Parkinson White (Type B) and congenital ichthyosis (Weiss) 133 (Letter to Editor)
- Echocardiograms aortic valve fine flutterings of the aortic valve as demonstrated by (Pinto et al) 807 (Annot)
- Echocardiographic features of the normal and malfunctioning porcine xenograft valve (Chandraratna and San Pedro) 548
- Echocardiography in chronic alcoholics following prolonged periods of abstinence (Reeves Nanda and Gramiak) 578
- Ectopia cordis (46,X,17q+) chromosome aberration in (Say and Wiley) 374 (Letter to Editor)
- Edema leg and nitroglycerin ointment therapy (Lee) 273 (Letter to Editor)
- myocardial a complication of ischemic arrest during cardio pulmonary bypass (Engelman) 128 (Annot)
- Effectiveness of the CCU (coronary care unit) more on (Fazzini Marchi and Pucci) 813 (Letter to Editor)
- Elderly patients with hip fractures can death from venous thromboembolism be prevented in? (Morris and Mitchell) 139
- the appropriate therapy of hypertension in (Barlow) 809 (Annot)
- Electric blanket electromagnetic interference in dynamic electrocardiography caused by an (Gascho and Newton) 408 (Annot)
- Electrocardiogram(s) exercise and treadmill exercise testing concepts and applications of (Farr McFerry and Morris) 102
- Frank lead electrode position effects on (Berson Haisty and Pipberger) 463
- orthogonal in normal women Implications of sex differences in diagnostic electrocardiography (Nemati et al) 12
- significance of a terminal R wave in Lead V of the (Raunio et al) 702
- Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia report of a patient with normal coronary arteriograms (Chavira et al) 637
- conduction aspects of hypokalemia prominent in a patient with periodic paralysis (Johnson and Catlin) 359
- Electrocardiography computerized (Jordy) 135 (Letter to Editor)
- diagnostic sex differences in implications of Orthogonal electrocardiogram in normal women (Nemati et al) 12
- dynamic electromagnetic interference in caused by an electric blanket (Gascho and Newton) 408 (Annot)

- Electrode position effects on Frank lead electrocardiograms (Berson Haisty and Pipberger) 463
- Electromagnetic interference in dynamic electrocardiography caused by an electric blanket (Gascho and Newton) 408 (Annot.)
- Electrophrenic respiration (diaphragm pacing) hemodynamic response to—Ordine's curve (Langou et al.) 295
- Electrophysiologic findings and clinical course in symptomatic sinus node dysfunction: vagal tone significance (Thormann et al.) 793
- Embolism pulmonary fatal inferior vena caval interruption in the prevention of (Gardner) 619
- Emergency room screening test for acute myocardial infarction usefulness and limitations of detection of myoglobin by radioimmunoassay in human sera as an (Gilleson et al.) 70
- Endocarditis bacterial: an analysis of factors affecting long term survival (McNeill Strong and Lockwood) 448
- Chlamydia trachomatis* (van der Bel Kahn et al.) 627
- polymicrobial infective: an increasing clinical entity (Sara volatz et al.) 163
- Endomyocardial biopsies from normal human hearts: incidence and significance of contraction bands in (Adomian, Laks and Billingham) 348
- Epidemiology importance of Rheumatic heart disease pentacosts and the (Ward) 266 (Annot.)
- Erythematous lupus systemic: a unique antibody response associated with the development of membranous nephropathy in (Frendl) 672 (Annot.)
- Essential hypertension: total effective compliance of the vascular bed in (London et al.) 375
- Etiology influence of on the functional result of aortic valve replacement (Hosack and Nelson) 454
- Excitation contraction abnormalities and heart block (Istanbul and Veldet) 275 (Letter to Editor)
- Exercise electrocardiogram and treadmill exercise testing: concepts and applications of (Farns McHenry and Morris) 107
- on the amplitude of the first heart sound in normal subjects effects of (Hume and Reuben) 4
- testing silent myocardial ischemia during and after in patients with coronary artery disease (Landsey and Cohen) 441
- treadmill and the exercise electrocardiogram: concepts and applications of (Farns McHenry and Morris) 107
- significance of hypotension developing during (Levites Baker and Anderson) 747
- tolerance and platelet aggregation effects on after abrupt propranolol withdrawal in angina pectoris (Frishman et al.) 169
- F
- Failing artificial pacemakers influence of atrial activity on ventricular capture by I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 507
- of atrial systole on: entricular capture by II Experimental observations (Abernathy Ferner and Moe) 489
- Failure heart chronic congestive role of the central nervous system in (Burch) 255
- FDA for surgery needed an? (Schoenfeld) 540 (Letter to Editor)
- Fibrillation atrial and atrial flutter lidocaine-induced cardiac rate changes in (Danahy and Aronow) 474
- threshold: entricular and carbon monoxide in dogs with acute myocardial injury (Aronow et al.) 754
- effect of vagus nerve stimulation on (Holman Verrier and Lown) 137 (Letter to Editor)
- Reply (Han and Lown) 139
- entricular (VF) in the conscious dog: effects of psychological stress and vagal stimulation with morphine on vulnerability to (DeSilva Verrier and Lown) 19
- Fibrin deposition on a pacemaker catheter in a heparinized patient (MacMillan and Strate) 405 (Annot.)
- Fibrinolysis natural (Browne) 417
- Fine flutterings of the aortic valve as demonstrated by aortic valve echocardiograms (Pinto et al.) 807 (Annot.)
- First heart sound effects of exercise on the amplitude of the m normal subjects (Hume and Reuben) 4
- Fistulas hepatic arteriovenous and hereditary telangiectasia (Osler Weber Rendu disease) misdiagnosis of atrial septal defect in patients with (Radtke et al.) 735
- Flow collateral functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance (Cohen) 396
- Fluid pressure elevated cerebrospinal components of the hemodynamic response to (Brashers and Yu) 52
- Flutter atrial and atrial fibrillation lidocaine-induced cardiac rate changes in (Danahy and Aronow) 474
- Force abnormal P terminal in Lead V<sub>1</sub> on the significance of an (Chandrasekaran and Langer) 267 (Annot.)
- (46 XX 17q+) ectopia cordis chromosome aberration in (Say and Wiseley) 774 (Letter to Editor)
- Frank lead electrocardiograms electrode position effects on (Berson Haisty and Pipberger) 463
- Fructose and triglycerides (Halpern) 640 (Letter to Editor)
- Furosemide reactions to (Warren and Steinberg) 541 (Letter to Editor)
- Reply (Greenblatt) 542
- G
- Generations four affected in a family with hereditary bundle branch system defect (Stephan) 89
- Gradient aortic and aortic valvular area: prediction of by noninvasive techniques (Cousins Eddleman and Reeves) 308
- Graft patency ventriculogram and surgical venting correlations between significance of new Q waves after bypass grafting (Antistabian et al.) 429
- phlebotomy acute postoperative a rare cause of saphenous vein—coronary artery bypass failure (Bulkley and Hutchins) 757
- Grafting bypass significance of new Q waves after correlations between graft patency ventriculogram and surgical venting (Antistabian et al.) 429
- H
- Health curricula high school, more on (LaForge) 272 (Letter to Editor)
- Heart(s) block, excitation—contraction abnormalities and (Istanbul and Veldet) 275 (Letter to Editor)
- conducting tissue of the in Chagas myocarditis histopathology of the (Andrade et al.) 316
- disease creatine kinase isoenzymes in the assessment of (Roberts and Sobel) 521
- ischemic differences in metal content of the heart muscle in death from (Chupperfield and Chupperfield) 739
- menstruation and (Goodyear) 675 (Letter to Editor)
- Reply (Blood donors and coronary disease) (Seely) 675
- rheumatic pyodermitis and the importance of epidemiology (Ward) 266 (Annot.)
- failure chronic congestive role of the central nervous system in (Burch) 255
- Holiday and arrhythmias alcohol associated cardiac rhythm disorders (Ettinger et al.) 555
- muscle differences in metal content of in death from ischemic heart disease (Chupperfield and Chupperfield) 732
- normal human incidence and significance of contraction bands in endomyocardial biopsies from (Adomian Laks, and Billingham) 348



- Coronary—continued  
 care unit(s) (CCU) more on effectiveness of the (Pazzini Marchi and Pucci) 813 (Letter to Editor)  
 diet in the (Warren Alpert and Francis) 130 (Annot.)  
 differences in (O'Rourke) 270 (Letter to Editor)  
 collaterals effect of on left ventricular function at rest and during stress (Schwarz et al.) 570  
 functional value of in myocardial ischemia and therapeutic approach to enhance collateral flow (Cohen) 396  
 disease blood donors and (Seely) 675 (Letter to Editor) (Reply to Goodyear p 675)  
 hemodynamics and ventricular function after intravenous nitroglycerin in coronary artery disease (Strauer and Scherpe) 210  
 occlusion acute effect of chronic cardiac denervation on infarct size following (Jones et al.) 738  
 Creatine kinase isoenzymes in the assessment of heart disease (Roberts and Sobel) 521  
 phosphokinase MB isoenzyme in hypothermia case reports and experimental studies (Carlson Emulson and Rapoport) 32  
 CRP WBC and BSR following cardiac pacemaker implant increase of (Yokoyama) 671 (Annot.)  
 Curricula high school health more on (LaForge) 272 (Letter to Editor)
- D
- Death(s) from venous thromboembolism be prevented in elderly patients with hip fractures can? (Morris and Mitchell) 138  
 sudden cardiac angina pectoris and myocardial infarction with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkeley Klacsmann and Hutchins) 563  
 from IHD by age and sex (Hodes) 413 (Letter to Editor)  
 Defibrillation threshold ventricular in dogs effect of pentobarbital anesthesia on (Babbs) 331  
 Definition of terms related to cardiac rhythm (WHO/ISC Task Force—see also de Medina et al.) 796 (Special report)  
 Denervation cardiac effect of chronic on infarct size following acute coronary occlusion (Jones et al.) 738  
 Deposition fibrin on a pacemaker catheter in a heparinized patient (MacMillan and Strate) 405 (Annot.)  
 Desert to each according to his (Scherf and Cohen) 336 (Annot.)  
 Diaphragm pacing (electrophoretic respiration) hemodynamic response to—Ondine's curse (Langou et al.) 295  
 Diastolic and systolic pressure and left ventricular work of (Burch) 406 (Annot.)  
 Diet in the Coronary Care Unit (Warren Alpert and Francis) 130 (Annot.)  
 Difference(s) in Coronary Care Units (O'Rourke) 270 (Letter to Editor)  
 vector the assessment of effects of changes or interventions (Nelson et al.) 220  
 Differential refractoriness of ventricular specialized conduction system (Tenczer and Littmann) 270 (Letter to Editor)  
 Direct measurements of stenosed coronary arteries in dogs comparison of coronary arteriograms with (Gallagher Foltz and Rowe) 338  
 Discussion on hypertrophic cardiomyopathy a (Clinical pathologic conference) (Spray et al.) 511  
 Disease heart menstruation and (Goodyear) 675 (Letter to Editor)  
 Reply (Blood donors and coronary disease) (Seely) 675  
 Diuretics thiazide mechanism of antihypertensive effect of (Shah Khatri and Freis) 611  
 Dobutamine a new inotropic agent in patients following cardiac surgery measurement of the circulatory effects of (Lewis et al.) 301
- Dog # tails—references? (Kennedy) 274 (Letter to Editor)  
 Donors blood and coronary disease (Seely) 675 (Letter to Editor) (Reply to Goodyear p 675)  
 Drug therapy Management of shock following acute myocardial infarction I (Kuhn) 529  
 Duchenne muscular dystrophy sequence of cardiac changes in (Heymfield et al.) 283  
 Dynamic electrocardiography electromagnetic interference in caused by an electric blanket (Gascho and Newton) 408 (Annot.)  
 Dysfunction left ventricular MIAP LVEDP and (Haddad and Prokhov) 814 (Letter to Editor)  
 Reply (Kouchoukos and Karp) 814  
 thyroid the systolic time intervals in (Burckhardt et al.) 187  
 Dystrophy Duchenne muscular sequence of cardiac changes in (Heymfield et al.) 283
- E
- Early open mitral commissurotomy a plea for (Spencer) 608  
 Ebstein's anomaly clinical classification of (Takayasu Obunai and Konno) 154  
 Wolff Parkinson White (Type B) and congenital ichthyosis (Weiss) 133 (Letter to Editor)  
 Echocardiograms aortic valve fine fluttering of the aortic valve as demonstrated by (Pinto et al.) 807 (Annot.)  
 Echocardiographic features of the normal and malfunctioning porcine xenograft valve (Chandraratna and San Pedro) 548  
 Echocardiography in chronic alcoholics following prolonged periods of abstinence (Reeves Nanda and Gramiak) 578  
 Ectopia cordis (46 XX 17q+) chromosome aberration in (Say and Walsey) 274 (Letter to Editor)  
 Edema leg and nitroglycerin ointment therapy (Lee) 2/3 (Letter to Editor)  
 myocardial a complication of ischemic arrest during cardiac pulmonary bypass (Engelman) 128 (Annot.)  
 Effectiveness of the CCU (coronary care unit) more on (Pazzini Marchi and Pucci) 813 (Letter to Editor)  
 Elderly patients with hip fractures can death from venous thromboembolism be prevented in? (Morris and Mitchell) 139  
 the appropriate therapy of hypertension in (Barlow) 809 (Annot.)  
 Electric blanket electromagnetic interference in dynamic electrocardiography caused by an (Gascho and Newton) 408 (Annot.)  
 Electrocardiogram(s) exercise and treadmill exercise testing concepts and applications of (Faris McHenry and Morris) 102  
 Frank lead electrode position effects on (Berson Hawley and Pipberger) 463  
 orthogonal in normal women Implications of sex differences in diagnostic electrocardiography (Nemati et al.) 12  
 significance of a terminal R wave in Lead V of the (Raunio et al.) 702  
 Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia report of a patient with normal coronary arteriograms (Chawla et al.) 637  
 conduction aspects of hypokalemia prominent in a patient with periodic paralysis (Johnson and Catlin) 359  
 Electrocardiography computerized (Pordy) 133 (Letter to Editor)  
 diagnostic sex differences in implications of Orthogonal electrocardiogram in normal women (Nemati et al.) 12  
 dynamic electromagnetic interference in caused by an electric blanket (Gascho and Newton) 408 (Annot.)

- Interventions or changes assessment of effects of--the difference vector (Nelson et al.) 220
- Intra atrial Wenckebach proximal effects of on distal atrioventricular nodal and His Purkinje block With special reference to the theory of alternating Wenckebach periods (Castellanos et al.) 228
- Intrapulmonary acetylcholine in bilateral cor pulmonale (Abdel Fattah et al.) 141
- Ionescu Shiley pericardial xenograft in the mitral position hemodynamic evaluation of the (Tandon Smith, and Ionescu) 595
- Ischemia myocardial, functional value of coronary collaterals in and therapeutic approach to enhance collateral flow (Cohen) 396
- Islet myocardial during and after exercise testing in patients with coronary artery disease (Landsey and Cohn) 441
- Ischemic arrest during cardiopulmonary bypass myocardial edema a complication of (Engelman) 128 (Annot)
- Islet heart disease differences in metal content of the heart muscle in death from (Chopperfield and Chopperfield) 739
- Islet myocardium post extrasystolic potentiation of by atrial stimulation (Diamond et al.) 204
- Isoenzyme(s) creatine kinase in the assessment of heart disease (Roberts and Sobel) 521
- MB creatine phosphokinase in hypothermia case reports and experimental studies (Carlson Emulson and Rapaport) 359
- Isolated T wave alternans (Navarro Lopez et al.) 369
- Isopterol stress in patients with aortic valve disease before and after corrective surgery cardiac reserve during (Schwarz et al.) 146

## A

- Kinase isoenzymes creatine in the assessment of heart disease (Roberts and Sobel) 521
- Kinin system and hemodynamics in acute myocardial infarction changes in components of (Hashimoto et al.) 611

## L

- Lead V abnormal P terminal force in on the significance of an (Chandraratna and Langevin) 267 (Annot)
- of the electrocardiogram significance of a terminal R wave in (Raunio et al.) 109
- Left anterior hemiblock overdiagnosis of (Neurath) 675 (Letter to Editor)
- Atrial activation indirect recording of in the main pulmonary trunk (Puech) 412 (Letter to Editor)
- Reply (Amat y Leon and Rosen) 413
- ventricular dysfunction MLAP LVEDP and (Haddad and Prokhov) 814 (Letter to Editor)
- Reply (Kouchoukos and Karp) 814
- function at rest and during stress effect of coronary collaterals on (Schwarz et al.) 570
- work of diastolic and systolic pressure and (Burch) 406 (Annot)
- Leg edema and nitroglycerin ointment therapy (Lee) 273 (Letter to Editor)
- Lidocaine induced cardiac rate changes in atrial fibrillation and atrial flutter (Danahy and Aronow) 474
- Lone aortic regurgitation aortic valve prostheses rheumatic fever and (Klothe) 5 (Letter to Editor)
- Long term survival in bacterial endocarditis an analysis of factors affecting (McNeill Strong and Lockwood) 444
- Low renin (primary) hyperaldosteronism clinical biochemical and pathological features of (Ferriss et al.) 3
- Differential diagnosis and distinction of sub-groups within the syndrome (Ferriss et al.) 641
- Lupus erythematosus, systemic a unique antibody response associated with the development of membranous nephropathy in (Friend) 62 (Annot)

- LVEDP MLAP and left ventricular dysfunction (Haddad and Prokhov) 814 (Letter to Editor)
- Reply (Kouchoukos and Karp) 814

## M

- Major medical centers preceptorships at (Livingston) 413 (Letter to Editor)
- Man of the mind of (Burch) 269 (Annot)
- Management of shock following acute myocardial infarction Part I Drug therapy (Kuhn) 9
- Part II Mechanical circulatory assistance (Kuhn) 789
- Maneuver Valsalva evaluation of the heart rate response to the (Kalbfleisch, Stowe and Smith) 707
- Mapping precordial ST segment use of (Madias) 96
- Marathonizing statistics and CHD (Milvy) 538 (Annot)
- Massive myocardial necrosis in a young woman (Nemickas et al.) 766 (Clinical pathologic conference)
- Materials, plastic in clinical medicine (Burch) 127 (Annot)
- MB isoenzyme creatine phosphokinase in hypothermia case reports and experimental studies (Carlson Emulson and Rapaport) 359
- Mechanical circulatory assistance Management of shock following acute myocardial infarction Part II (Kuhn) 789
- Mechanism of antihypertensive effect of thiazide diuretics (Shah Khatri and Fries) 611
- of concealed trigeminy (Kinoshita) 410 (Letter to Editor)
- Reply (Tracy) 411
- Medical Centers major preceptorships at (Livingston) 413 (Letter to Editor)
- management contemporary of stable angina pectoris (Sostman and Langou) 770
- Medicine clinical, of plastic materials in (Burch) 127 (Annot)
- Membranous nephropathy in systemic lupus erythematosus a unique antibody response associated with the development of (Friend) 62 (Annot)
- Menstruation and heart disease (Goodyear) 675 (Letter to Editor)
- Reply (Blood donors and coronary disease) (Seely) 675
- Metal content of the heart muscle in death from ischemic heart disease differences in (Chopperfield and Chopperfield) 739
- Microvascular changes analgesic abuse and (Abrahams Furman and Salant) 268 (Annot)
- Mind of man of the (Burch) 269 (Annot)
- Mitral commissurotomy early open a plea for (Spencer) 668
- position hemodynamic evaluation of the Ionescu Shiley pericardial xenograft in the (Tandon Smith and Ionescu) 595
- regurgitation and myocardial infarction single coronary artery with (Newton and Burwell) 16 (Annot)
- systolic murmurs four year follow up of Black schoolchildren with non-ejection systolic clicks and (Cohen et al.) 697
- valve prolapse coronary artery spasm and (Buda et al.) 457
- MLAP LVEDP and left ventricular dysfunction (Haddad and Prokhov) 814 (Letter to Editor)
- Reply (Kouchoukos and Karp) 814
- More on effectiveness of the CCU (coronary care unit) (Fazzini Marchi and Pucci) 813 (Letter to Editor)
- on high school health curricula (LaForge) 11 (Letter to Editor)
- Morphine effects of psychological stress and vagal stimulation on vulnerability to ventricular fibrillation (VF) in the conscious dog (DeSilva Verner and Lown) 197
- Muscular dystrophy Duchenne sequence of cardiac changes in (Heymansfield et al.) 283

Heart(s)—continued

- one of why the two heart pumps are anatomically united to form (Burch) 811 (Annot)
- pumps two of why the are anatomically united to form one heart (Burch) 811 (Annot)
- rat an experimental study in the isolated showing a possible role of noradrenaline in the development of myocardial infarction (Waldenström Hjalmarsen and Thornell) 43
- rate response to the Valsalva maneuver evaluation of the (Kalbfleisch Stowe and Smith) 707
- sound in normal subjects first effects of exercise on the amplitude of (Hume and Reuben) 4
- valve replacement artificial cholethiasis a frequent complication of (Harrison et al) 483
- Hemiblock left anterior overdiagnosis of (Neurath) 675 (Letter to Editor)
- Hemodynamics and kinn system in acute myocardial infarction changes in components of (Hashimoto et al) 619
- coronary and ventricular function after intravenous nitroglycerin in coronary artery disease (Strauer and Scherpe) 210
- evaluation of the Jones Shiley pericardial xenograft in the mitral position (Tandon Smith and Jones) 595
- response to diaphragm pacing (electrophrenic respiration)—Ondine's curse (Langou et al) 295
- to elevated cerebrospinal fluid pressure components of the (Brashear and Yu) 52
- Heparinized patient fibrin deposition on a pacemaker catheter in a (MacMillan and Strate) 405 (Annot)
- Hepatic arteriovenous fistulas and hereditary telangiectasia (Osler Weber Rendu disease) misdiagnosis of atrial septal defect in patients with (Radtke et al) 235
- Hereditary bundle branch system defect Survey of a family with four affected generations (Stephan) 89
- Q T interval prolongation (Romano Ward syndrome) autonomic maneuvers in (Curtiss Heibel and Shaver) 420
- telangiectasia (Osler Weber Rendu disease) and hepatic arteriovenous fistulas misdiagnosis of atrial septal defect in patients with (Radtke et al) 235
- High school health curricula more on (LaForge) 272 (Letter to Editor)
- Hip fractures can death from venous thromboembolism be prevented in elderly patients with? (Morris and Mitchell) 139
- His Purkinje and distal atrioventricular nodal block effects of proximal atrial Wenckebach on With special reference to the theory of alternating Wenckebach periods (Castellanos et al) 228
- Histopathology of the conducting tissue of the heart in Chagas myocarditis (Andrade et al) 316
- Holiday Heart and arrhythmias Alcohol associated cardiac rhythm disorders (Ettinger et al) 555
- Home or to hospital at? (Donaldson) 406 (Annot)
- Hospital at home or to? (Donaldson) 406 (Annot)
- Hydralazine the comeback of (Koch Wester) 1
- Hygiene of teaching (Burch) 535 (Annot)
- Hyperaldosteronism low renin (primary) clinical biochemical and pathological features of (Ferriss et al) 375
- Differential diagnosis and distinction of subgroups within the syndrome (Ferriss et al) 641
- Hyperkalemia electrocardiographic changes simulating acute myocardial infarction caused by report of a patient with normal coronary arteriograms (Chawla et al) 637
- Hypertension appropriate therapy of in the elderly (Barlow) 809 (Annot)
- complex the (Mendlovitz) 389
- essential total effective compliance of the vascular bed in (London et al) 325
- non specific aorto arteritis in Singapore with special reference to (Teoh et al) 683

Hypertension—continued

- systemic after surgical treatment of a congenital aortic valve malformation (Rocchini et al) 497
  - Hypertensive patients effect of saralasin upon plasma catecholamines in (Vlachakis Ribeiro and Krakoff) 78
  - Hypertrophic cardiomyopathy a discussion on (Clinical pathologic conference) (Spray et al) 511
  - Hypokalemia prominent electrocardiographic conduction aspects of in a patient with periodic paralysis (Johnson and Catlin) 359
  - Hypotension developing during treadmill exercise testing significance of (Levites Baker and Anderson) 747
  - Hypothermia creatine phosphokinase MB isoenzyme in case reports and experimental studies (Carlson Emilson and Rapaport) 352
- I
- Ichthyosis congenital Wolff Parkinson White (Type B) and Ebstein's anomaly (Weiss) 133 (Letter to Editor)
  - IHD sudden deaths from by age and sex (Hodes) 413 (Letter to Editor)
  - Implant cardiac pacemaker increase of WBC CRP and BSR following (Yokovama) 671 (Annot)
  - Infarct size following acute coronary occlusion effect of chronic cardiac denervation on (Jones et al) 738
  - Infarction acute myocardial caused by hyperkalemia electrocardiographic changes simulating report of a patient with normal coronary arteriograms (Chawla et al) 637
  - changes in components of kinn system and hemodynamics in (Hashimoto et al) 619
  - management of shock following Part I Drug therapy (Kuhn) 529
  - Part II Mechanical circulatory assistance (Kuhn) 789
  - significance of nausea and vomiting during (Ahmed Gupta and Brancato) 671 (Annot)
  - and mitral regurgitation angle coronary artery with (Newton and Burwell) 126 (Annot)
  - and preinfarction angina relationship between a histopathological study of coronary arteries in two sudden death cases employing serial section (Horie Sekiguchi and Hiroswa) 81
  - angina pectoris and sudden cardiac death with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klagsmann and Hutchins) 563
  - in the Black population of South Africa coronary arteriographic findings (Chester et al) 691
  - possible role of noradrenaline in the development of an experimental study in the isolated rat heart (Waldenström Hjalmarsen and Thornell) 43
  - radionuclides in the assessment of (Klein Roberts and Coleman) 659
  - Infective endocarditis polymicrobial an increasing clinical entity (Saravolatz et al) 163
  - Inferior vena caval interruption in the prevention of fatal pulmonary embolism (Gardner) 679
  - Influence of etiology on the functional result of aortic valve replacement (Hossack and Neilson) 454
  - Indirect recording of left atrial activation in the main pulmonary trunk (Puech) 412 (Letter to Editor)
  - Reply (Amat y Leon and Rosen) 413
  - Inotropic agent dobutamine a new in patients following cardiac surgery measurement of the circulatory effects of (Leiva et al) 301
  - Interference electromagnetic in dynamic electrocardiography caused by an electric blanket (Gascho and Newton) 408 (Annot)
  - International cardiology (Goodwin) 279
  - Interval prolongation Q T hereditary (Romano Ward syndrome) autonomic maneuvers in (Curtiss Heibel and Shaver) 420

Paralysis periodic prominent electrocardiographic conduction aspects of hypokalemia in a patient with (Johnson and Catinchi) 359

Parasystole and re-entry (Kinoshta) 81\* (Letter to Editor) Reply (Laghtfoot) 813

Paroxysmal atrioventricular junctional reentrant tachycardia antegrade and retrograde conduction characteristics in 3 patterns of (Akhtar et al.) 22

Pathological clinical and biochemical features of low renin (primary) hyperaldosteronism (Ferriss et al.) 375

Pectoris angina abrupt propranolol withdrawal in effects on platelet aggregation and exercise tolerance (Frishman et al.) 169

myocardial infarction and sudden cardiac death with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klagsmann and Hutchins) 563

Pentobarbital anesthesia on ventricular defibrillation threshold in dogs, effect of (Babbs) 331

Pericardial xenograft, Ionescu Shiley in the mitral position hemodynamic evaluation of the (Tandon, Smith and Ionescu) 595

Periodic paralysis prominent electrocardiographic conduction aspects of hypokalemia in a patient with (Johnson and Catinchi) 359

Pharmacology studies human with a new orally active stimulant of cardiac adrenergic beta receptors (Knaus et al.) 602

Phlebitis acute postoperative graft a rare cause of saphenous vein-coronary artery bypass failure (Bulkley and Hutchins) 757

Phosphokinase creatine MB isoenzyme in hypothermia case reports and experimental studies (Carlson, Emilson and Rapaport) 332

Plasma catecholamines in hypertensive patients effect of saralasin upon (Vlachakis Ribeiro and Krakoff) 78

Plastic materials in clinical medicine of (Burch) 127 (Annot)

Platelet aggregation and exercise tolerance effects on after abrupt propranolol withdrawal in angina pectoris (Frishman et al.) 169

Plea for early open mitral commissurotomy a (Spencer) 668

Polymicrobial infective endocarditis an increasing clinical entity (Saravolatz et al.) 163

Porcine xenograft valve echocardiographic features of the normal and malfunctioning (Chandraratna and San Pedro) 548

Post-extrasystolic potentiation of ischemic myocardium by atrial stimulation (Diamond et al.) 204

Postoperative graft phlebitis, acute a rare cause of saphenous vein-coronary artery bypass failure (Bulkley and Hutchins) 757

Potassium and salt substitutes (Haddad) 134 (Letter to Editor)

Prazosin (Therapy) (Lowenstein and Steele) 767

Preceptorships at major medical centers (Livingston) 413 (Letter to Editor)

PreCORD ST segment mapping use of (Madhavi) 96

Prediction of aortic valvular area and gradient by noninvasive techniques (Cousins, Eddleman and Reeves) 308

Preinfarction angina relationship between myocardial infarction and A histopathological study of coronary arteries in two sudden death cases employing serial section (Horie, Sekiguchi, and Hirosewa) 81

Premature activation of the ventricular conduction system functional properties of the left septal Purkinje network in (Iwamura et al.) 60

Pressure arterial the variability of (Littler et al.) 180

cerebrospinal fluid elevated, components of the hemodynamic response to (Brashear and Yu) 52

of diastolic and systolic and left ventricular work (Burch) 406 (Annot)

Primary (low renin) hyperaldosteronism clinical biochemical, and pathological features of (Ferriss et al.) 375

Primary (low renin) hyperaldosteronism—continued

Differential diagnosis and distinction of sub-groups within the syndrome (Ferriss et al.) 641

Progressive systemic sclerosis a clinicopathologic study of 9 patients with angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries (Bulkley Klagsmann and Hutchins) 563

Prolapse mitral valve coronary artery spasm and (Buda et al.) 457

Prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis (Johnson and Catinchi) 359

Propranolol withdrawal in angina pectoris abrupt effects on platelet aggregation and exercise tolerance (Frishman et al.) 169

Prostheses, valve aortic ball arterial thromboembolic complications with (Boekhout Mussert et al.) 210 (Letter to Editor) Reply (Dale) 271

rheumatic fever and lone aortic regurgitation (Kloth) 275 (Letter to Editor)

Proximal intra atrial Wenckebach, effects of on distal atrioventricular nodal, and His Purkinje block With special reference to the theory of alternating Wenckebach periods (Castellanos et al.) 228

Pseudotumor rheumatic heart disease and the importance of epidemiology (Ward) 256 (Annot)

Psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog effects of (DeSilva, Verrier and Lown) 197

P terminal force in Lead V abnormal, on the significance of an (Chandraratna and Langevin) 267 (Annot)

Pulmonary embolism fatal inferior vena caval interruption in the prevention of (Gardner) 619

tree vascular report of a case of pulmonary varix with additional anomalies of the (Moro et al.) 243

trunk, main indirect recording of left atrial activation in the (Puech) 412 (Letter to Editor) Reply (Amat y Leon and Rosen) 413

varix report of a case with additional anomalies of the vascular pulmonary tree (Moro et al.) 243

vascular effects of verapamil (Davidson, McMurtry and Reeves) 810 (Annot)

Pumps, the two heart of why they are anatomically united to form one heart (Burch) 811 (Annot)

Purkinje network, left septal in premature activation of the ventricular conduction system functional properties of the (Iwamura et al.) 60

## Q

Q waves after bypass grafting significance of new correlations between graft patency ventriculogram and surgical venting (Antablian et al.) 479

Q T interval prolongation hereditary (Romano, Ward syndrome) autonomic maneuvers in (Curtiss, Heibel and Shaver) 470

## R

R wave terminal, in Lead V of the electrocardiogram significance of a (Raunio et al.) 707

Radiommonography for detection of myoglobin in human sera its usefulness and limitations as an emergency room screening test for acute myocardial infarction (Gukeson et al.) 70

Radiomorphology in the assessment of myocardial infarction (Klem, Roberts and Coleman) 659

Reactions to furosemide (Warren and Steinberg) 541 (Letter to Editor) Reply (Greenblatt) 542

Recording of left atrial activation indirect in the main pulmonary trunk (Puech) 412 (Letter to Editor) Reply (Amat y Leon and Rosen) 413

- Myocardial edema a complication of ischemic arrest during cardiopulmonary bypass (Engelman) 128 (Annot)
- infarction acute caused by hyperkalemia electrocardiographic changes simulating report of a patient with normal coronary arteriograms (Chawla et al) 637
- changes in components of kunn system and hemodynamics in (Hashimoto et al) 619
- management of shock following Part I Drug therapy (Kuhn) 529
- Part II Mechanical circulatory assistance (Kuhn) 789
- significance of nausea and vomiting during (Ahmed Gupta and Brancato) 671 (Annot)
- usefulness and limitations of detection of myoglobin by radioimmunoassay in human sera as an emergency room screening test for (Gilkeson et al) 70
- and mitral regurgitation single coronary artery with (Newton and Burwell) 126 (Annot)
- and preinfarction angina relationship between A histopathological study of coronary arteries in two sudden death cases employing serial section (Horie Sekiguchi and Hirose) 81
- angina pectoris and sudden cardiac death with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkley Klacsmann and Hutchins) 563
- in the Black population of South Africa coronary arteriographic findings (Chesler et al) 691
- possible role of noradrenaline in the development of An experimental study in the isolated rat heart (Waldenström Hjalmarsson and Thornell) 43
- radionuclides in the assessment of (Klein Roberts and Coleman) 659
- injury acute carbon monoxide and ventricular fibrillation threshold in dogs with (Aronow et al) 754
- ischemia functional value of coronary collaterals in and therapeutic approach to enhance collateral flow (Cohen) 396
- silent during and after exercise testing in patients with coronary artery disease (Lindsey and Cohn) 441
- necrosis massive in a young woman (Nemickas et al) 766 (Clinical pathologic conference)
- Myocarditis Chagas histopathology of the conducting tissue of the heart in (Andrade et al) 316
- Myocardium ischemic post extrasystolic potentiation of by atrial stimulation (Diamond et al) 204
- Myoglobin detection of by radioimmunoassay in human sera its usefulness and limitations as an emergency room screening test for acute myocardial infarction (Gilkeson et al) 70

N

- Natural fibrinolysis (Browne) 417
- Nausea and vomiting during acute myocardial infarction significance of (Ahmed Gupta and Brancato) 671 (Annot)
- Necrosis myocardial massive in a young woman (Nemickas et al) 766 (Clinical pathologic conference)
- Needed An FDA for surgery? (Schoenfeld) 540 (Letter to Editor)
- Nephropathy membranous in systemic lupus erythematosus a unique antibody response associated with the development of (Friend) 672 (Annot)
- Nerve stimulation vagus effect on ventricular fibrillation threshold (Holman Verner and Lown) 132 (Letter to Editor)
- Reply (Han and Yoon) 132
- Nervous system central role of the in chronic congestive heart failure (Burch) 255
- Nitroglycerin intravenous ventricular function and coronary hemodynamics after in coronary artery disease (Strauer and Scherpe) 210
- ointment therapy and leg edema (Lee) 273 (Letter to Editor)

- Nodosa panarthritis involvement of the cardiac conduction system in (Thiene Valente and Rossi) 716
- Node dysfunction sinus symptomatic vagal tone significance of electrophysiologic findings and clinical course in (Thormann et al) 725
- Non ejection systolic clicks and mitral systolic murmurs four year follow up of Black schoolchildren with (Cohen et al) 697
- Noninvasive techniques prediction of aortic valvular area and gradient by (Cousins Eddleman and Reeves) 308
- Non specific aorta arteritis in Singapore with special reference to hypertension (Teoh et al) 683
- Noradrenaline in the development of myocardial infarction possible role of An experimental study in the isolated rat heart (Waldenström Hjalmarsson and Thornell) 43
- Nutritional repletion cardiac abnormalities in esophageal patients before and during (Heymsfield et al) 584

O

- Occlusion coronary acute effect of chronic cardiac denervation on infarct size following (Jones et al) 738
- Of diastolic and systolic pressure and left ventricular work (Burch) 406 (Annot)
- plastic materials in clinical medicine (Burch) 127 (Annot)
- teaching hygiene (Burch) 530 (Annot)
- the mind of man (Burch) 269 (Annot)
- sham operation (Burch) 674 (Annot)
- why the two heart pumps are anatomically united to form one heart (Burch) 811 (Annot)
- Ointment therapy nitroglycerin and leg edema (Lee) 273 (Letter to Editor)
- Ondine's Curse Hemodynamic response to diaphragm pacing (electrophrenic respiration) (Langou et al) 295
- One heart of why the two heart pumps are anatomically united to form (Burch) 811 (Annot)
- Open mitral commissurotomy early a plea for (Spencer) 668
- Operation of the sham (Burch) 674 (Annot)
- Orally active stimulant of cardiac adrenergic beta receptors new human pharmacology studies with a (Knaus et al) 602
- Orthogonal electrocardiogram in normal women the implications of sex differences in diagnostic electrocardiography (Nemati et al) 12
- Ossler Weber Rendu disease (hereditary telangiectasia) and hepatic arteriovenous fistulas misdiagnosis of atrial septal defect in patients with (Radtke et al) 235
- Overdiagnosis of left anterior hemiblock (Neurath) 675 (Letter to Editor)

P

- Pacemaker(s) and pacing cardiac IX Statistical analysis of pacemaker data (Furman and Whitman) 115
- catheter fibrin deposition on in a heparinized patient (MacMillan and Strate) 405 (Annot)
- data statistical analysis of Cardiac pacing and pacemakers IX (Furman and Whitman) 115
- failing artificial influence of atrial activity on ventricular capture by I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 502
- of atrial systole on ventricular capture by II Experimental observations (Abernathy Ferner and Moe) 469
- implant cardiac increase of WBC CRP and BSR following (Yokoyama) 671 (Annot)
- salvage the at autopsy (Rossi) 540 (Letter to Editor)
- Pacing and pacemakers cardiac IX Statistical analysis of pacemaker data (Furman and Whitman) 115
- diaphragm (electrophrenic respiration) hemodynamic response to—Ondine's curse (Langou et al) 295
- Panarthritis nodosa involvement of the cardiac conduction system in (Thiene Valente and Rossi) 716

- Paroxysmal periodic prominent electrocardiographic conduction aspects of hypokalemia in a patient with (Johnson and Catuchin) 359
- Paroxysmal and re-entry (Kinoshita) 819 (Letter to Editor)
- Reply (Lightfoot) 813
- Paroxysmal atrioventricular junctional reentrant tachycardia antegrade and retrograde conduction characteristics in 3 patterns of (Akhtar et al) 2
- Pathological clinical and biochemical features of low renin (primary) hyperaldosteronism (Ferriss et al) 35
- Pectus antrum abrupt propranolol withdrawal in effects on platelet aggregation and exercise tolerance (Frishman et al) 169
- myocardial infarction and sudden cardiac death with normal coronary arteries a clinicopathologic study of 9 patients with progressive systemic sclerosis (Bulkeley Klacsmann and Hutchins) 563
- Pentobarbital anesthesia on ventricular defibrillation threshold in dogs, effect of (Babbs) 331
- Pericardial xenograft Ionescu Shiley in the mitral position hemodynamic evaluation of the (Tandon Smith and Ionescu) 595
- Periodic paralysis prominent electrocardiographic conduction aspects of hypokalemia in a patient with (Johnson and Catuchin) 359
- Pharmacology studies human with a new orally active stimulant of cardiac adrenergic beta receptors (Knaus et al) 602
- Phlebitis acute postoperative graft a rare cause of saphenous vein-coronary artery bypass failure (Bulkeley and Hutchins) 757
- Phosphokinase creatine MB isoenzyme in hypothermia case reports and experimental studies (Carlson Emilson, and Rapoport) 352
- Plasma catecholamines in hypertensive patients effect of saralasin upon (Vlachakis Ribeiro and Krakoff) 78
- Plastic materials in clinical medicine of (Burch) 127 (Annot)
- Platelet aggregation and exercise tolerance effects on after abrupt propranolol withdrawal in angina pectoris (Frishman et al) 169
- Plea for early open mitral commissurotomy a (Spencer) 568
- Polymicrobial infective endocarditis an increasing clinical entity (Saravolatz et al) 163
- Purkinje xenograft valve echocardiographic features of the normal and malfunctioning (Chandraratna and San Pedro) 543
- Post-extrasystolic potentiation of ischemic myocardium by atrial stimulation (Diamond et al) 204
- Postoperative graft phlebitis acute a rare cause of saphenous vein-coronary artery bypass failure (Bulkeley and Hutchins) 757
- Potassium and salt substitutes (Haddad) 134 (Letter to Editor)
- Prazosin (Therapy) (Lowenstein and Steele) 269
- Preceptionships at major medical centers (Livingston) 413 (Letter to Editor)
- Precordial ST-segment mapping use of (Madans) 96
- Prediction of aortic valvular area and gradient by noninvasive techniques (Cousins Eddleman and Reeves) 308
- Preinfarction angina relationship between myocardial infarction and A histopathological study of coronary arteries in two sudden death cases employing serial section (Horie Sekiguchi, and Hirosewa) 81
- Premature activation of the ventricular conduction system functional properties of the left septal Purkinje network in (Iwamura et al) 60
- Pressure arterial the variability of (Littler et al) 180
- cerebrospinal fluid elevated components of the hemodynamic response to (Brashers and Yu) 5
- of diastolic and systolic and left ventricular work (Burch) 406 (Annot)
- Primary (low renin) hyperaldosteronism clinical, biochemical, and pathological features of (Ferriss et al) 355
- Primary (low renin) hyperaldosteronism-continued
- Differential diagnosis and distinction of sub groups within the syndrome (Ferriss et al) 641
- Progressive systemic sclerosis, a clinicopathologic study of 9 patients with angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries (Bulkeley Klacsmann and Hutchins) 563
- Prolapse mitral valve coronary artery spasm and (Buda et al) 47
- Prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis (Johnson and Catuchin) 359
- Propranolol withdrawal in angina pectoris abrupt effects on platelet aggregation and exercise tolerance (Frishman et al) 163
- Prostheses, valve aortic ball, arterial thromboembolic complications with (Boekhout Mussert et al) 210 (Letter to Editor)
- Reply (Dale) 271
- rheumatic fever and lone aortic regurgitation (Kloth) 275 (Letter to Editor)
- Proximal intra atrial Wenckebach, effects of on distal atrioventricular nodal and His Purkinje block With special reference to the theory of alternating Wenckebach periods (Castellanos et al) 228
- Pulsatilis rheumatic heart disease and the importance of epidemiology (Ward) 286 (Annot)
- Psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog effects of (DeSilva Verrier and Lowry) 197
- P terminal force in Lead V, abnormal on the significance of an (Chandraratna and Langevin) 267 (Annot)
- Pulmonary embolism fetal inferior vena caval interruption in the prevention of (Gardner) 619
- tree vascular report of a case of pulmonary varix with additional anomalies of the (Moro et al) 243
- trunk main indirect recording of left atrial activation in the (Puech) 412 (Letter to Editor)
- Reply (Amat y Leon and Rosen) 413
- varix report of a case with additional anomalies of the vascular pulmonary tree (Moro et al) 243
- vascular effects of verapamil (Davidson McMurtry and Reeves) 810 (Annot)
- Pumps the two heart of why they are anatomically united to form one heart (Burch) 811 (Annot)
- Purkinje network left septal in premature activation of the ventricular conduction system functional properties of the (Iwamura et al) 60
- Q waves after bypass grafting significance of new correlations between graft patency ventriculogram and surgical venting (Ainabian et al) 49
- Q T interval prolongation hereditary (Romano Ward syndrome) autonomic maneuvers in (Curtiss Heibel and Shaver) 420
- R
- R wave terminal in Lead V of the electrocardiogram significance of a (Raunio et al) 709
- Radiomunoassay for detection of myoglobin in human sera its usefulness and limitations as an emergency room screening test for acute myocardial infarction (Gilkeson et al) 70
- Rachonuchides in the assessment of myocardial infarction (Klein Roberts and Coleman) 659
- Reactions to furosemide (Warren and Steinberg) 541 (Letter to Editor)
- Reply (Greenblatt) 542
- Recording of left atrial activation indirect in the main pulmonary trunk (Puech) 412 (Letter to Editor)
- Reply (Amat y Leon and Rosen) 413

## Subject index

- Re entry and parasystole (Kinoshita) 812 (Letter to Editor)  
Reply (Lightfoot) 813
- References—dog's tails? (Kennedy) 274 (Letter to Editor)
- Refractoness differential of ventricular specialized conduction system (Tenczer and Littmann) 270 (Letter to Editor)
- Regurgitation lone aortic aortic valve prostheses rheumatic fever and (Kloth) 275 (Letter to Editor)  
mitral and myocardial infarction single coronary artery with (Newton and Burwell) 126 (Annot)
- Repletion nutritional cardiac abnormalities in cachectic patients before and during (Heymsfield et al) 584
- Research venture (Seely) 133 (Letter to Editor)
- Respiration electrophrenic (diaphragm pacing) hemodynamic response to—Ondine's curse (Langou et al) 295
- Retrograde Wenckebach phenomenon in ventricular tachycardia (Cotoi Georgescu and Coslea) 676 (Letter to Editor)
- Rheumatic fever aortic valve prostheses and lone aortic regurgitation (Kloth) 275 (Letter to Editor)  
heart disease psittacosis and the importance of epidemiology (Ward) 266 (Annot)
- Rhythm cardiac definition of terms related to (WHO/ISC Task Force—see also de Medina et al) 796 (Special report)
- disorders cardiac alcohol associated arrhythmias and the Holiday Heart (Ettlinger et al) 555
- Romano Ward syndrome (hereditary Q T interval prolongation) autonomic maneuvers in (Curtiss Heibel and Shaver) 420
- S
- Salt substitutes and potassium (Haddad) 134 (Letter to Editor)
- Salvage the pacemaker at autopsy (Rossi) 540 (Letter to Editor)
- Saphenous vein—coronary artery bypass failure acute postoperative graft phlebitis a rare cause of (Bulkeley and Hutchins) 757
- Saralasin upon plasma catecholamines in hypertensive patients effect of (Vlachakis Ribeiro and Krakoff) 78
- Schoolchildren black with non ejection systolic clicks and mitral systolic murmurs four year follow up of (Cohen et al) 697
- Sclerosis progressive systemic a clinicopathologic study of 9 patients with angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries (Bulkeley Kiacsmann and Hutchins) 563
- Septal defect atrial misdiagnosis of in patients with hereditary telangiectasia (Osler Weber Rendu disease) and hepatic arteriovenous fistulas (Radtko et al) 235
- Purkinje network left in premature activation of the ventricular conduction system functional properties of the (Iwamura et al) 60
- Sera human detection of myoglobin by radioimmunoassay in its usefulness and limitations as an emergency room screening test for acute myocardial infarction (Giles et al) 70
- Sex and age sudden deaths from IHD by (Hodes) 413 (Letter to Editor)  
differences in diagnostic electrocardiography implications of Orthogonal electrocardiogram in normal women (Nemati et al) 12
- Sham operation of the (Burch) 674 (Annot)
- Shock following acute myocardial infarction management of Part I Drug therapy (Kuhn) 529  
Part II Mechanical circulatory assistance (Kuhn) 789
- Silent myocardial ischemia during and after exercise testing in patients with coronary artery disease (Lindsey and Cohn) 441
- Singapore non specific aorto arteritis in with special reference to hypertension (Teoh et al) 683
- Single coronary artery with myocardial infarction and mitral regurgitation (Newton and Burwell) 126 (Annot)
- Sinus node dysfunction symptomatic vagal tone significance of electrophysiologic findings and clinical course in (Thormann et al) 725
- Spasm coronary artery and mitral valve prolapse (Buda et al) 457
- Specialized conduction system ventricular differential refractoriness of (Tenczer and Littmann) 270 (Letter to Editor)
- ST segment mapping use of precordial (Madias) 96
- Stable angina pectoris contemporary medical management of (Sostman and Langou) 775
- Statistical analysis of pacemaker data Cardiac pacing and pacemakers IV (Furman and Whitman) 115
- Statistics marathon and CHD (Milvy) 538 (Annot)
- Stenosed coronary arteries in dogs comparison of coronary arteriograms with direct measurements of (Gallagher Folts and Rowe) 338
- Stress effect of coronary collaterals on left ventricular function at rest and during (Schwarz et al) 570
- Substitutes salt and potassium (Haddad) 134 (Letter to Editor)
- Sudden cardiac death angina pectoris and myocardial infarction with normal coronary arteries a clinicopathologic study of 11 patients with progressive systemic sclerosis (Bulkeley Kiacsmann and Hutchins) 563
- deaths from IHD by age and sex (Hodes) 413 (Letter to Editor)
- Surgery needed an FDA for? (Schoenfeld) 540 (Letter to Editor)
- Surgical treatment of a congenital arteriovenous malformation systemic hypertension after (Rocchini et al) 497
- venting graft patency and ventriculogram correlations between significance of new Q waves after bypass grafting (Amabile et al) 429
- Survival long term in bacterial endocarditis an analysis of factors affecting (McNeill Strong and Lockwood) 448
- Symptomatic sinus node dysfunction vagal tone significance of electrophysiologic findings and clinical course in (Thormann et al) 725
- Syndrome—low renin (primary) hyperaldosteronism—differential diagnosis and distinction of subgroups within the (Ferriss et al) 641
- System central nervous role of the in chronic congestive heart failure (Burch) 255
- Systemic hypertension after surgical treatment of a congenital arteriovenous malformation (Rocchini et al) 497
- lupus erythematosus a unique antibody response associated with the development of membranous nephropathy in (Friend) 672 (Annot)
- sclerosis progressive a clinicopathologic study of 9 patients with angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries (Bulkeley Kiacsmann and Hutchins) 563
- Systole atrial on ventricular capture by failing artificial pacemakers influence of II Experimental observations (Abernathy Ferrer and Moe) 489
- Systolic and diastolic pressure and left ventricular work of (Burch) 406 (Annot)
- clicks non ejection and mitral systolic murmurs four year follow up of Black schoolchildren with (Cohen et al) 697
- murmurs mitral four year follow up of Black schoolchildren with non-ejection systolic clicks and (Cohen et al) 697
- time intervals in thyroid dysfunction the (Burckhardt et al) 187

## T

- wave alternans isolated (Navarro Lopez et al.) 369  
 tachycardia, paroxysmal atrioventricular junctional reentrant antegrade and retrograde conduction characteristics in II patterns of (Akhtar et al.) 22  
 ventricular retrograde Wenckebach phenomenon in (Coto, Georgescu, and Cozlea) 676 (Letter to Editor)  
 tails dogs—references? (Kennedy) 774 (Letter to Editor)  
 teaching hygiene of (Burch) 535 (Annot)  
 elongectasia hereditary (Osler Weber Rendu disease) and hepatic arteriovenous fistulas misdiagnosis of atrial septal defect in patients with (Radtke et al.) 235  
 terminal II wave in Lead V of the electrocardiogram significance of a (Raunio et al.) 107  
 terms related to cardiac rhythm definition of (WHO/ISC Task Force—see also de Medina et al.) 796 (Special report)  
 the hypertension complex (Mendlowitz) 389  
 therapy appropriate of hypertension in the elderly (Barlow) 609 (Annot)  
 nitroglycerin ointment and leg edema (Lee) 273 (Letter to Editor)  
 thiazide diuretics mechanism of antihypertensive effect of (Shah Khatri and Fries) 611  
 threshold, ventricular defibrillation in dogs effect of pentobarbital anesthesia on (Babbs) 331  
 thromboembolic complications arterial with aortic ball valve prostheses (Boekhout Mussert et al.) 210 (Letter to Editor)  
 Reply (Dale) 271  
 thromboembolism venous can death from be prevented in elderly patients with hip fractures? (Morris and Mitchell) 139  
 thyroid dysfunction the systolic time intervals in (Burchhardt et al.) 187  
 time intervals systolic in thyroid dysfunction the (Burchhardt et al.) 187  
 to each according to his desert (Scherf and Cohen) 536 (Annot)  
 hospital, or at home? (Donaldson) 406 (Annot)  
 treadmill exercise testing and the exercise electrocardiogram concepts and applications of (Faris McHenry and Morris) 107  
 significance of hypotension developing during (Levites Baker and Anderson) 747  
 tricuspid atresia simulated tricuspid valve echoes in (Silverman Payot and Stanger) 761  
 valve echoes simulated in tricuspid atresia (Silverman Payot and Stanger) 761  
 trigeminy concealed mechanism of (Kinoshiba) 410 (Letter to Editor)  
 Reply (Levy) 411  
 triglycerides and fructose (Halpern) 540 (Letter to Editor)  
 trunk pulmonary main inferior recording of left atrial activation in the (Puech) 417 (Letter to Editor)  
 Reply (Amat y Leon and Rosen) 413  
 two heart pumps are anatomically united to form one heart of why the (Burch) 811 (Annot)

## V

- Vagal stimulation and psychological stress with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog effects of (DeSilva Verner and Lown) 197  
 tone significance of electrophysiologic findings and clinical course in symptomatic sinus node dysfunction (Thormann et al.) 77  
 vagus nerve stimulation on ventricular fibrillation threshold effect of (Kolman Verner and Lown) 137 (Letter to Editor)  
 Reply (Han and Yoon) 139  
 valsalva maneuver evaluation of the heart rate response to the (Kaltfleisch Stowe and Smith) 701

- Valve aortic fine flutterings of as demonstrated by aortic valve echocardiograms (Pinto et al.) 807 (Annot)  
 disease aortic cardiac reserve during isoproterenol stress in patients with before and after corrective surgery (Schwarz et al.) 146  
 echoes tricuspid simulated in tricuspid atresia (Silverman Payot and Stanger) 761  
 porcine xenograft echocardiographic features of the normal and malfunctioning (Chandraratna and San Pedro) 548  
 prolapse mitral, coronary artery spasm and (Buda et al.) 457  
 prostheses aortic ball arterial thromboembolic complications with (Boekhout Mussert et al.) 210 (Letter to Editor)  
 Reply (Dale) 271  
 rheumatic fever and lone aortic regurgitation (Kloth) 275  
 replacement, aortic influence of etiology on the functional result of (Hossack and Neilson) 454  
 heart, artificial cholelithiasis a frequent complication of (Harrison et al.) 483  
 Valvular area aortic and gradient prediction of by noninvasive techniques (Cousins Eddleman and Reeves) 308  
 Variability of arterial pressure the (Lettler et al.) 180  
 Varix pulmonary report of a case with additional anomalies of the vascular pulmonary tree (Moro et al.) 243  
 Vascular bed in essential hypertension total effective compliance of the (London et al.) 325  
 effects of verapamil, pulmonary (Davidson McMurtry and Reeves) 810 (Annot)  
 pulmonary tree report of a case of pulmonary varix with additional anomalies of the (Moro et al.) 243  
 Vector difference assessment of effects of changes or interventions (Nelson et al.) 220  
 Vena caval interruption inferior in the prevention of fatal pulmonary embolism (Gardner) 679  
 Venous thromboembolism can death from be prevented in elderly patients with hip fractures? (Morris and Mitchell) 139  
 Ventricular afterload a succinct yet comprehensive definition (Noordergraaf and Melbin) 545  
 capture by failing artificial pacemakers influence of atrial activity on I Report of two new cases and review of the literature (Abernathy and Lepeschkin) 407  
 influence of atrial systole on II Experimental observations (Abernathy Ferner and Moe) 489  
 conduction system functional properties of the left septal Purkinje network in premature activation of the (Iwamura et al.) 60  
 defibrillation threshold in dogs effect of pentobarbital anesthesia on (Babbs) 331  
 dysfunction left MLAP LV EDP and (Haddad and Prokhorov) 814 (Letter to Editor)  
 Reply (Kouchoukos and Karp) 814  
 fibrillation threshold and carbon monoxide in dogs with acute myocardial injury (Aronow et al.) 754  
 effect of vagus nerve stimulation on (Kolman Verner and Lown) 132 (Letter to Editor)  
 Reply (Han and Yoon) 139  
 (VF) in the conscious dog effects of psychological stress and vagal stimulation with morphine on vulnerability to (DeSilva Verner and Lown) 197  
 function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease (Strauer and Scherpe) 210  
 left at rest and during stress, effect of coronary collaterals on (Schwarz et al.) 570  
 specialized conduction system differential refractoriness of (Tenczer and Littmann) 211 (Letter to Editor)  
 tachycardia retrograde Wenckebach phenomenon in (Coto, Georgescu and Cozlea) 676 (Letter to Editor)



## Subject index

- Ventricular—continued
  - work left of diastolic and systolic pressure and (Burch) 406 (Annot)
- Ventriculogram graft patency and surgical venting correlations between significance of new Q waves after bypass grafting (Aintabhan et al) 429
- Venture research (Seely) 133 (Letter to Editor)
- Verapamil pulmonary vascular effects of (Davidson McMurry and Reeves) 810 (Annot)
- Vomiting and nausea during acute myocardial infarction significance of (Ahmed Gupta and Brancato) 671 (Annot)

## W

- Wave T alternans isolated (Navarro Lopez et al) 369
- WBC CRP and BSR following cardiac pacemaker implant increase of (Yokoyama) 671 (Annot)
- Wenckebach periods alternating special reference to the theory of Effects of proximal intra atrial Wenckebach on distal atrioventricular nodal and His Purkinje block (Castellanos et al) 228

## Wenckebach—continued

- phenomenon retrograde in ventricular tachycardia (Cotoi Georgescu and Cozlea) 676 (Letter to Editor)
- proximal intra atrial effects of on distal atrioventricular nodal and His Purkinje block With special reference to the theory of alternating Wenckebach periods (Castellanos et al) 228
- Wolff Parkinson White (Type B) Ebstein's anomaly and congenital ichthyosis (Weiss) 133 (Letter to Editor)
- Work left ventricular of diastolic and systolic pressure and (Burch) 406 (Annot)

## X

- Xenograft Ionescu Shiley pericardial in the mitral position hemodynamic evaluation of the (Tandon Smith and Ionescu) 595
- valve porcine echocardiographic features of the normal and malfunctioning (Chandraratna and San Pedro) 548

Your confidence in Intermedics is as important to us as your patient's confidence is to you. That's why we want you to know about the InterLith<sup>®</sup> chosen around the world as one of the most reliable pacemakers available.

Intermedics supports the outstanding reliability of the InterLith and will allow a replacement on model 223 generators which fail for any reason during the lifetime of the original user.

Extensive use has confirmed its outstanding performance and reliability resulting in an annual failure rate of only .003 at the 90% confidence level with no reported failures of its lithium power source.

In addition to its proven reliability, the InterLith has significant features which make it an especially fine choice as a replacement pacemaker such as a universal connector that readily accepts most leads without an adapter. So when your patient needs a pacemaker for whatever reason, consider the InterLith model 223 a pacemaker with which you can feel confident.

**Confidence begins with extraordinary design features.** A tungsten inert gas (TIG) welding technique is used to hermetically seal the InterLith in a 316L stainless steel enclosure that prevents moisture leakage. A specially designed polycrystalline ceramic feedthrough seal utilizing a 99.99% pure platinum conductor makes the electrical connection to the pulse generator. The high collar design of the feedthrough minimizes fluid leakage in the harsh environment of the human body.

The patient lifetime replacement agreement is limited to the standard model 223 pulse generator and does not include the 223-02 (High-Output) pulse generator. Consult the physician's handbook for these "special" pacemakers for their specific patient replacement agreements.

The InterLith is one of the smallest, lightest pacemakers on the market. Its corners are gently beveled much as the contours of the patient's own body, minimizing the risk of pressure necrosis. The unipolar model weighs only 75 grams and measures 6.0 cm by 4.6 cm by 1.5 cm, enabling a smaller incision and a more cosmetic pocket for greatest patient comfort. The InterLith pacemaker provides the physician with an ideal choice for many pacing situations.

### **Confidence increases with superior performance**

The InterLith's annual failure rate of less than .003 (at 90% confidence level) is largely attributable to the outstanding longevity of its lithium power cell—a battery without a single failure reported in 150,000 battery units manufactured. Combined with the proven reliability of CMOS circuitry, the InterLith provides superior performance at the lowest possible power consumption. This design represents sophisticated state-of-the-art technology in pacemaker electronics and gives the InterLith an outstanding theoretical longevity.

### **Quality control ensures confidence**

Every component utilized in the InterLith is selected and tested to meet the same standards as in the most exacting aerospace and military applications. Every step of the manufacturing process at Intermedics is subject to rigid quality assurance procedures in our complete environmental testing

laboratory because at Intermedics we believe only the highest quality products can merit your confidence. Some of the high reliability screening steps that our pacemakers receive in manufacturing are:

1. Twenty-four hour dynamic temperature cycling from -30° to +80°C
2. Vibration testing at 1 displacement and 10 g's from 20 Hz to 2 KHz
3. Strip chart rate recording from room temperature to 60°C
4. Hermetic seal testing to 4 x 10<sup>-6</sup> atm cc/sec



**The InterLith is designed and built for the confidence of you and your patients.**

So the next time one of your patients requires pacing therapy, why not select the InterLith? Where reliability counts, there's no better choice.



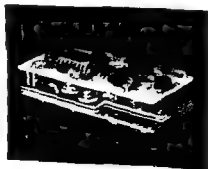
**Intermedics Inc.**

P.O. Box 617  
Freeport, Texas 77541

## **Our business is life**

InterLith is a trademark of Intermedics Inc., Freeport, Texas.

©1976 Intermedics Inc., Freeport, Texas 77541



## *Subject index*

### **Ventricular—continued**

- work left of diastolic and systolic pressure and (Burch) 406 (Annot )
- Ventriculogram graft patency and surgical venting correlations between significance of new Q waves after bypass grafting (Amthabian et al ) 429
- Venture research (Seely ) 133 (Letter to Editor)
- Verapamil pulmonary vascular effects of (Davidson McMurry and Reeves) 810 (Annot )
- Vomiting and nausea during acute myocardial infarction significance of (Ahmed Gupta and Brancato) 671 (Annot )

## **W**

- Wave T alternans isolated (Navarro Lopez et al ) 369
- WBC CRP and BSR following cardiac pacemaker implant increase of (Yokoyama) 671 (Annot )
- Wenckebach periods alternating special reference to the theory of Effects of proximal intra atrial Wenckebach on distal atrioventricular nodal and His Purkinje block (Castellanos et al ) 228

### **Wenckebach—continued**

- phenomenon retrograde in ventricular tachycardia (Cotoi Georgescu and Cozlea) 676 (Letter to Editor)
- proximal intra atrial effects of on distal atrioventricular nodal and His Purkinje block With special reference to the theory of alternating Wenckebach periods (Castellanos et al ) 228
- Wolff Parkinson White (Type B) Ebstein's anomaly and congenital ichthyosis (Weiss) 133 (Letter to Editor)
- Work left ventricular of diastolic and systolic pressure and (Burch) 406 (Annot )

## **X**

- Xenograft Ionescu Shiley pericardial in the mitral position hemodynamic evaluation of the (Tandon Smith and Ionescu) 595
- valve porcine echocardiographic features of the normal and malfunctioning (Chandraratna and San Pedro) 548





